

the fifth and eighth day in the fourth litter, the third and the fifth day in the fifth litter and the fourth and the sixth day in the sixth and seventh litters.

Opening of Eyes: According to Donaldson the eyes open on the fourteenth to the seventeenth day, most often on the fifteenth or sixteenth day. King⁹ has also observed that in a given litter the eyes of the females usually open several hours before those of the males. In our test animals of the second generation the eyes opened on the fourteenth day in the rats born of the prepubertal group and in the first two litters of the mature group. The time varied between the twelfth and the fourteenth day in the third, fourth, fifth, sixth and seventh litters.

Descent of Testes: In the offspring of the thymus-treated rats of the second generation, the testes descended earlier than in normal rats. Thus in the prepubertal group the descent of the testes occurred from the twenty-third to the twenty-ninth day. In the mature group there is a progressive acceleration in the descent of the testes. In the first litter it occurred at 29 days, in the second at 28 days, in the third, fourth, fifth and sixth at 21 and 22 days and in the seventh at 15 days.

Opening of Vagina: In all the offspring of thymus-treated rats of the second generation, the vagina opened earlier than normal. In the litters born of the group treated prepubertally the vagina opened on the thirtieth day. In the offspring of the group treated after maturity it opened on the thirty-fifth day in the first, second and fourth litters, on the forty-second day in the fifth litter, on the thirty-second day in the third and sixth litters and on the thirtieth day in the seventh litter.

Growth Curve of Animals of the Second Generation: The growth curve of the later litters show a decided increase in weight over the normal. Figure 1 shows the growth curve of the control animals and of the first, fifth and tenth litters of the second generation of test animals.

Because of the possibility of great significance attaching to the data relating to the tenth litter from the original mature test pair (rats 20 and 21) these data are presented here despite the fact that this litter was born subsequent to the preparation of the body of this report (April 16, 1934). This litter of 4 had a birth weight of 5.2 Gm. The ears opened on the second day; the teeth erupted on the second day; hair obscured the genitalia between the sixth and the tenth days; the eyes opened on the tenth day; the testes descended on the twelfth day, and the vagina opened on the thirtieth day. These figures indicate considerable precocity in the development of the tenth litter born to thymus-treated parents.

Summary of Data Relative to the Second Generation.—The foregoing data show that as a result of treatment of the parents the young

9. King, H. D.: Anat. Rec. **27**:337, 1924.

ARCHIVES OF INTERNAL MEDICINE

EDITORIAL BOARD

ARTHUR BLOOMFIELD, San Francisco

N. C. GILBERT, Chicago

REGINALD FITZ, Boston

J. H. MUSSER, New Orleans

RUSSELL M. WILDER, Rochester, Minn.

VOLUME 56
1935

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILL.

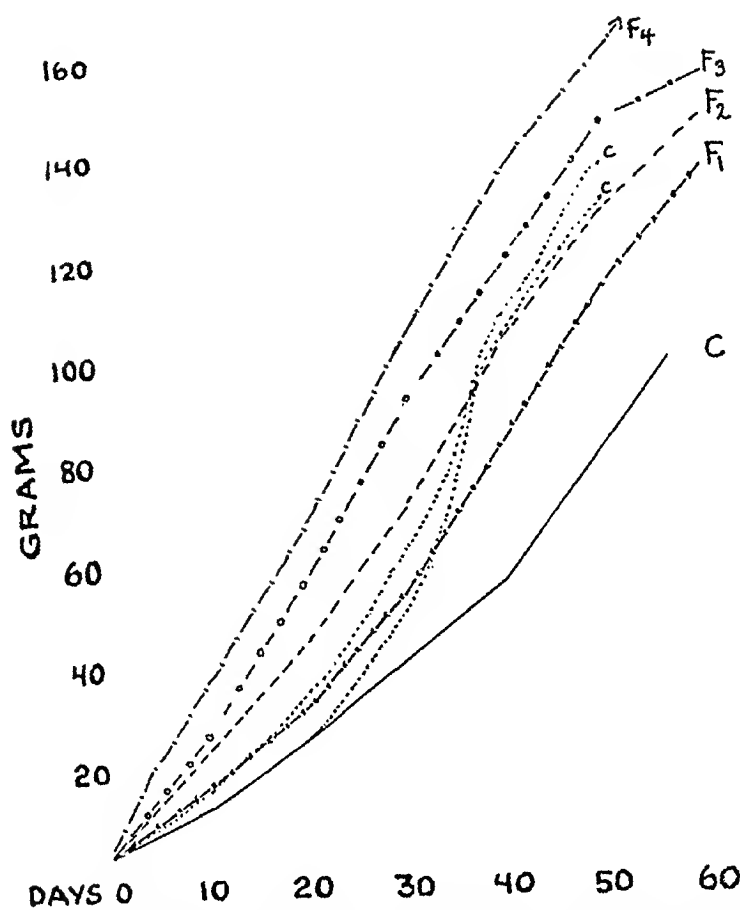


Fig. 5.—Curves showing weight of thymus-treated rats and of control animals.

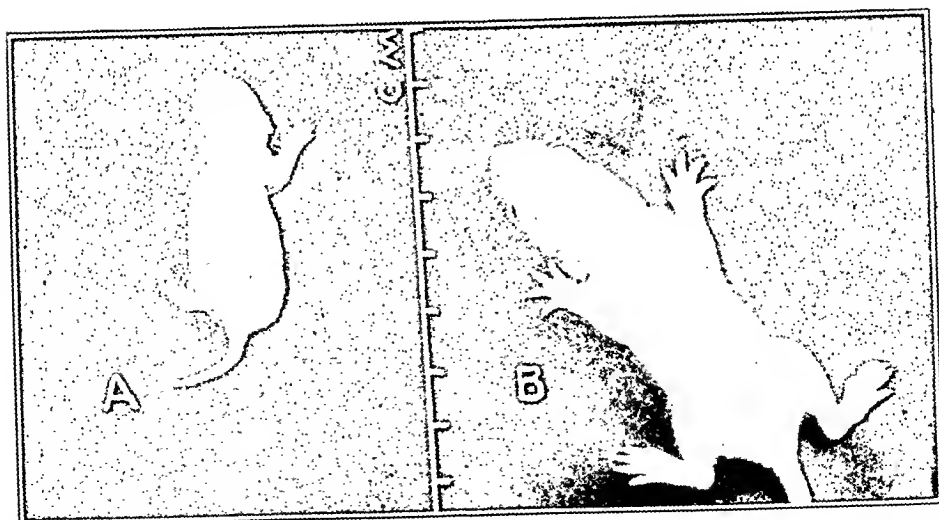


Fig. 6.—Seventh generation rats: *A*, control, 3 days old; *B*, thymus-treated, 45 hours old. The eyes of the thymus-treated rat are open.

A number of the patients in both groups complained of shortness of breath on exertion. In only one patient (G. N.) was there definite edema of the ankles. One patient (A. V.) had auricular fibrillation. In an attempt to control the effect of these cardiac difficulties we tested two women with mitral stenosis, both of whom were short of breath on exertion but neither of whom was edematous. It will be seen that the cost of work in these two subjects was within normal limits.

One patient with myxedema was also tested, and the results are included for purposes of comment.

COMMENT

No matter what method is used in comparing the efficiency of walking in patients with hyperthyroidism with that of patients with leukemia it becomes obvious that the two groups are quite different.

Plummer and Boothby concluded that hyperthyroidism "is associated not only with a characteristic increase in the number of useless extraneous movements but further each movement requires approximately twice the normal amount of energy for its accomplishment. Muscular tissue with a resting metabolism increased above normal by thyroxin cannot utilize any portion of this extra heat for the production of motion."

Smith found that patients with hyperthyroidism used more oxygen in holding up a weight than did normal subjects. Plummer and Boothby studied six patients with exophthalmic goiter; Smith studied twelve subjects with toxic goiter, and we have studied eight patients in whom hypermetabolism can be attributed to increase of thyroid secretion. The results are in accord in that patients with hyperthyroidism require an excessive amount of oxygen to accomplish a given amount of work. Our data do not show, as did those of Plummer and Boothby, that "each movement requires approximately twice the normal amount of oxygen for its accomplishment." Even the most casual observation of these two groups of patients on the treadmill leads one to the conclusion that patients with hyperthyroidism are wasteful of oxygen because of increased muscle tone and purposeless movements. It seems possible that an increase in muscle tone and extraneous movements may account for the 38 per cent increase in oxygen used by our subjects with hyperthyroidism in walking. This explanation would obviate the necessity for assuming any basic change in the chemical mechanism of muscle contraction.

Two of the patients with hyperthyroidism (G. F. and T. H.) had been receiving compound solution of iodine before the tests were made. The basal metabolic rate decreased from 67 per cent above normal to 7 per cent above normal in G. F., and the exact amount of decrease in T. H. is not known. In both subjects the cost of work was high.

CONTENTS OF VOLUME 56

JULY 1935. NUMBER 1

	PAGE
Biologic Effects of Thymus Extract (Hanson): Accruing Acceleration in Growth and Development in Five Successive Generations of Rats Under Continuous Treatment with Thymus Extract. L. G. Rowntree, M.D., and J. H. Clark, M.D., Philadelphia, and A. M. Hanson, M.D., Faribault, Minn., with the Technical Assistance of Arthur Steinberg, B.S., Philadelphia	1
Cost of Work in Patients with Hypermetabolism Due to Leukemia and to Exophthalmic Goiter. Stella Paisley Briard, M.S.; J. T. McClintock, M.D., and C. W. Baldrige, M.D., Iowa City.....	30
Treatment of Congestive Heart Failure and Angina Pectoris by Total Ablation of the Normal Thyroid Gland: XVI. The Sensitivity of Man to Epinephrine Injected Intravenously Before and After Total Thyroidectomy. J. E. F. Riseman, M.D.; D. R. Gilligan, M.S., and H. L. Blumgart, M.D., Boston	38
Circulatory Changes in Angina Pectoris: An Experimental Study. Philip Shambaugh, M.D., Boston.....	59
Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of Left Ventricle: Electrocardiographic Characteristics. Charles Christian Wolf-ferth, M.D., and Francis Clark Wood, M.D., with the Collaboration of Samuel Bellet, M.D., Philadelphia.....	77
Action of Oil of Peppermint on the Secretion and Motility of the Stomach in Man. Jacob Meyer, M.D.; Louis Scheman, M.D., and H. Necheles, M.D., Ph.D., Chicago	88
Acute Carbon Tetrachloride Poisoning: Report of a Case. Earl R. Lehnherr, M.D., Boston.....	98
Progress in Internal Medicine:	
Diseases of the Adrenal Glands: A Review with Special Reference to the Clinical Aspects. Edwin J. Kepler, M.D., Rochester, Minn.....	105
Disease of the Thyroid Gland: An Interpretative Review of Progress Toward Solution of the Problem. Walter M. Boothby, M.D., Rochester, Minn.....	136
Book Reviews.....	207

AUGUST 1935. NUMBER 2

Pathology of the Vessels of the Pulmonary Circulation: Part I. O. Brenner, M.D., M.R.C.P., Birmingham, England.....	211
Cardiovascular Complications of Trichinosis. Wesley W. Spink, M.D., Boston.	238
Obstructing Pericarditis: Effect of Resection of the Pericardium on the Circulation of a Patient with Concretio Cordis. C. Sidney Burwell, M.D., and D. Flickinger, M.D., Nashville, Tenn.....	250
Pulmonary Tuberculosis of the Lower Lobe. David Reisner, M.D., New York.	258
Stab Wounds of the Heart: A Study of Electrocardiographic Changes, Polyserositis (Pick's Syndrome) and Pericarditis. John D. Koucky, M.D., and George Milles, M.D., Chicago.....	281
Infection and Hemorrhagic Nephritis. Walter L. Winkenwerder, M.D.; Neil McLeod, M.D., and Myles Baker, M.D., Baltimore.....	297
The Viscerogalvanic Reaction. E. A. Spiegel, M.D., and M. G. Wohl, M.D., Philadelphia	327
Effect of Diuretics on the Cardiac Output of Patients with Congestive Heart Failure. Ben Friedman, M.D., New York; Harry Resnik Jr., M.D., Nashville, Tenn.; J. A. Calhoun, M.D., Boston, and T. R. Harrison, M.D., Nashville, Tenn.....	341

respiratory quotients for the patients with leukemia were exceedingly low. However, the respiratory quotients for these few patients varied so much that conclusions drawn from a study of them would be of doubtful value.

We have not found the secret of the economy in muscular movement displayed by some patients with leukemia. We have demonstrated a definite difference between the hypermetabolism of exophthalmic goiter and that of leukemia. This difference affords a reasonable explanation for the fact that patients with marked hypermetabolism due to leukemia can work and yet maintain their body weight fairly well without the excessive appetite usually seen in patients with exophthalmic goiter.

The results obtained in the one case of myxedema are of special interest because of the number of patients with cardiac disease who are being subjected to total ablation of the thyroid gland. The patient with myxedema converted calories to kilogram-meters of work very efficiently, as 25 per cent of the total energy produced during walking (including the oxygen debt) would have been necessary to raise and to lower the body if the efficiency in transforming calories to kinetic energy had been 100 per cent. In the patients with leukemia only about 15 per cent of the total energy would have been necessary to raise and to lower the body, and the figure was also 15 per cent for the patients with mitral stenosis. Less than 10 per cent of the total energy produced by the patients with hyperthyroidism would have been necessary to raise and to lower the body if an efficiency of 100 per cent could have been attained. In these calculations it was considered that the energy necessary to lower the body was 52 per cent of that necessary to raise it.¹³

SUMMARY

In eleven patients with leukemia the basal metabolic rate varied from 13 to 57 per cent above normal (average, + 38 per cent). The cost of walking varied from 12 per cent above normal to 33 per cent below normal (average of twenty-three tests, — 8.5 per cent). The average metabolism while standing was 18 per cent above the average basal metabolic rate (normal, about 12 per cent).

In eight patients with exophthalmic goiter the basal metabolic rate varied from 13 to 67 per cent above normal (average, + 40 per cent). The cost of walking varied from 13 to 53 per cent above normal (average of twenty tests, + 38 per cent). The average metabolism while standing was 23 per cent above the average basal metabolic rate. One patient with myxedema (basal metabolic rate, — 42 per cent) used 19 per cent less energy than normal in walking.

13. Amar, Jules: *The Human Motor*, London, G. Routledge & Sons, 1920. p. 359.

CONTENTS OF VOLUME 56

AUGUST—Continued

	PAGE
Teaching Medical Students Objectives for Care of Patients and Social Aspects of Illness. Ethel Cohen, M.S., and Harry A. Derow, M.D., Boston.....	351
Increased Effectiveness of Insulin when Given by Injections of Doses of Equal Unitage at Intervals of Two to Four Hours: I. Use of Insulin in Divided Doses to Manage Severe Uncomplicated Diabetes and to Control Complicated Medical Cases. Byron B. Clark, Ph.D.; R. B. Gibson, Ph.D., and William D. Paul, M.D., Iowa City.....	360
Influence of Di-Nitrophenol on Carbohydrate Metabolism. Max Wishnofsky, M.D.; Arthur P. Kane, M.D.; Edmund L. Shlevin, M.D., and Charles S. Byron, M.D., Brooklyn.....	374
Progress in Internal Medicine:	
Infectious Diseases: Review of the Current Literature. Hobart A. Reimann, M.D., Minneapolis.....	382
Book Reviews.....	412
News and Comment.....	412

SEPTEMBER 1935. NUMBER 3

Treatment of Severe Diabetic Acidosis: A Comparison of Methods, with Particular Reference to the Use of Racemic Sodium Lactate. Alexis F. Hartmann, M.D., with the Technical Assistance of Marie Morton, St. Louis.....	413
Differential Diagnosis Between Cerebral Hemorrhage and Cerebral Thrombosis: A Clinical and Pathologic Study of 245 Cases. Charles D. Aring, M.D., and H. Houston Merritt, M.D., Boston.....	435
Pathology of the Vessels of the Pulmonary Circulation: Part II. O. Brenner, M.D., M.R.C.P., Birmingham, England.....	457
Urticaria Due to Sensitivity to Cold: Survey of the Literature and Report of a Case, with Experimental Observations. Harold D. Levine, M.D., Boston.	498
Experimental Concentric and Eccentric Cardiac Hypertrophy in Rats. David A. Rytand, M.D., and W. Dock, M.D., San Francisco.....	511
Studies of Hepatic Function: II. In Portal Cirrhosis and Congestive Heart Failure. A. Cantarow, M.D., Philadelphia.....	521
Progress in Internal Medicine:	
Peripheral Vascular Diseases: A Review of Some of the Recent Literature with a Critical Review of Surgical Treatment. George W. Scupham, M.D., and Géza de Takáts, M.D., Chicago.....	530
Book Reviews.....	623

OCTOBER 1935. NUMBER 4

Etiology and Treatment of Sprue: Observations on Patients in Puerto Rico and Subsequent Experiments on Animals. W. B. Castle, M.D., Boston; C. P. Rhoads, M.D., New York; H. A. Lawson, M.D., Providence, R. I., and G. C. Payne, M.D., San Juan, Puerto Rico.....	627
Clinical Experience with a Derivative of Squill. James G. Carr, M.D., and Jacob D. Mayer, M.D., Chicago.....	700
Effect of Digitalis on the Cardiac Output of Persons with Congestive Heart Failure. Ben Friedman, M.D., New York, and Gurney Clark, M.D.; Harry Resnik Jr., M.D., and T. R. Harrison, M.D., Nashville, Tenn.....	710
Pathology of the Vessels of the Pulmonary Circulation: Part III. O. Brenner, M.D., M.R.C.P., Birmingham, England.....	724
Pulmonary Abscess and Pulmonary Gangrene: Analysis of Ninety Cases Observed in Ten Years. B. S. Kline, M.D., and S. S. Berger, M.D., Cleveland	753
Treatment of Cardiovascular Syphilis: A Study of the Duration of Life in Eighty Treated and Untreated Patients with Aortic Aneurysm and Aortic Regurgitation. Ernest K. Stratton, M.D., San Francisco.....	773

on the coronary suture. Four-tenths cubic centimeter of a 1:10,000 solution of epinephrine was injected without disturbing the animal. A constant traction of 50 Gm. was applied to the suture without evidence of discomfort. This dose of epinephrine was followed by the typical reaction of moderate severity. With the subminimal pull still in effect, the heart rate was increased from 104 to 172 per minute by the intravenous injection of 0.54 mg. of atropine, the tachycardia occurring within twenty seconds but without any evidence of discomfort. The epinephrine was now repeated in the same dosage as before and was followed by a typical reaction, definitely more severe than before the onset of the tachycardia (fig. 13).

Increasing the heart rate by atropine in the presence of a subminimal traction on the coronary suture failed to precipitate the pain reaction in the foregoing experiments, whereas an elevation of the blood pressure by epinephrine in the same dogs and with the same degree of mechanical constriction of the coronary vessels produced the typical response. However, it was found that after the tachycardia had been established, a smaller dosage of epinephrine produced the reaction, and that the

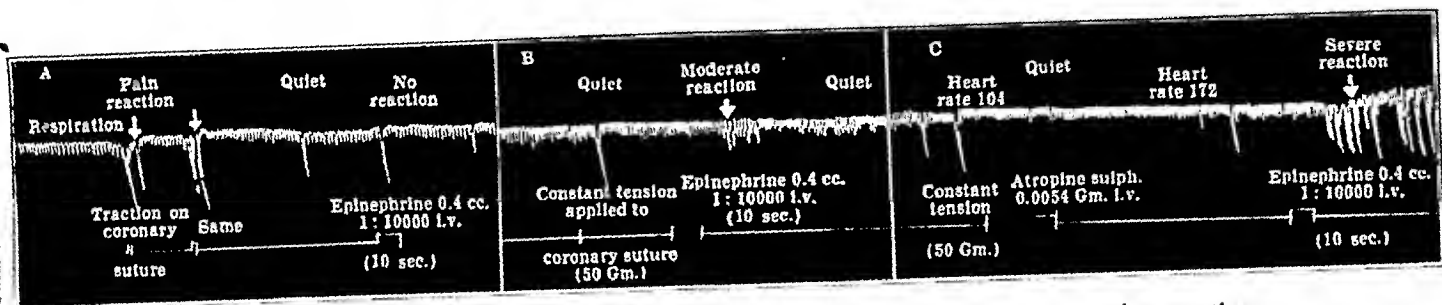


Fig. 13.—Tracing from dog C70. *A* shows a typical response to traction on the coronary suture, with no reaction to epinephrine alone; *B*, a positive reaction to epinephrine with subminimal traction on the suture, and *C*, no reaction to atropine with a subminimal traction on the suture, and increased reaction to epinephrine after atropinization.

reaction to a given effective dose of epinephrine was definitely more severe than previously.¹²

COMMENT

My observations on the effect of mechanical interference with the coronary blood flow in unanesthetized dogs are in accord with those of previous observers. There is a constant typical reaction which without doubt signifies pain. A graphic record of this reaction can be made only by noting changes in the respiratory tracing. This is, however, by no means an accurate record of the reaction as observed at the time

12. The increased effectiveness of epinephrine after atropinization may be due to (1) the fact that the vascular demands of the myocardium are already increased by the tachycardia or (2) the fact that the vasopressor response to epinephrine is somewhat greater with the vagus paralyzed (fig. 11), presumably owing to abolition of the depressor reflex.

OCTOBER—Continued

	PAGE
Relation of Asthma to Sinusitis, with Special Reference to the Results from Surgical Treatment. Robert A. Cooke, M.D., and R. Clark Grove, M.D., New York.....	779
Pyothorax Due to Fusospirochetal Infection. Russell A. Flack, M.D., Lafayette, Ind.....	790
Progress in Internal Medicine:	
Gastro-Enterology in 1934. Garnett Cheney, M.D., San Francisco.....	797
Book Reviews.....	831

NOVEMBER 1935. NUMBER 5

Cyclic Response of the Thyroid Gland to Experimental Excitation and Depression. Harry B. Friedgood, M.D., Boston.....	833
Normal Hematologic Standards. Edwin E. Osgood, M.D., Portland, Ore....	849
Rôle of Pressor Substances in Arterial Hypertension. R. B. Capps, M.D.; E. B. Ferris Jr., M.D.; F. H. L. Taylor, Ph.D., and Soma Weiss, M.D., Boston	864
The Renal Threshold for Dextrose in Man. James W. Sherrill, M.D., and Eaton M. MacKay, M.D., La Jolla, Calif.....	877
Effect of Low Caloric Diets and Resultant Loss in Weight on Plasma Cholesterol in the Obese. Charles A. Poindexter, M.D., and Maurice Bruger, M.D., New York.....	884
Effect of Certain Therapeutic Measures on the Cardiac Output of Patients with Congestive Heart Failure. Harry Resnik Jr., M.D., Nashville, Tenn.; Ben Friedman, M.D., New York, and T. R. Harrison, M.D., Nashville, Tenn.....	891
Effect of High Intrapleural Pressure on Blood Pressure. Jerome R. Head, M.D., Chicago.....	904
Acute Glomerulonephritis Following Pneumococcic Lobar Pneumonia: Analysis of Seven Cases. David Seegal, M.D., New York.....	912
Relationship of Pellagrous Dermatitis to Sunlight. Tom D. Spies, M.D., Cleveland	920
Interpretation of Abnormal Dextrose Tolerance Curves Occurring in Toxemia in Terms of Liver Function. S. Soskin, M.D.; M. D. Allweiss, M.D., and I. A. Mirsky, M.D., Chicago.....	927
Differential Diagnosis of Rubella: Use of the Schilling Differential Leukocyte Count. Cyril M. MacBryde, M.D., and Cecil M. Charles, M.D., St. Louis	935
Renal Amyloidosis: Clinical Course and Pathologic Lesions in Sixteen Cases. Hugo O. Altnow, M.D., Minneapolis, and Charlotte C. Van Winkle, M.D.; Henry W. Maly, M.D., and Lowell E. Williams, M.D., Oak Terrace, Minn.....	944
Pathology of the Vessels of the Pulmonary Circulation: Part IV. O. Brenner, M.D., M.R.C.P., Birmingham, England.....	976
Progress in Internal Medicine:	
Syphilis: A Review of the Recent Literature. Joseph Earle Moore, M.D., Baltimore	1015
Book Reviews.....	1066

DECEMBER 1935. NUMBER 6

Appearance of a Dengue-Like Fever in Northern California. Garnett Cheney, M.D., San Francisco.....	1067
Hyperglycemia and Glycosuria Associated with Disease of the Biliary Tract. Herman Lande, M.D., and Herbert Pollack, M.D., New York.....	1097
Idiopathic Steatorrhea: Metabolic Study of a Patient, with Reference to the Utilization of Nitrogen and Fat. James F. Weir, M.D., and Mildred Adams, Ph.D., Rochester, Minn.....	1109

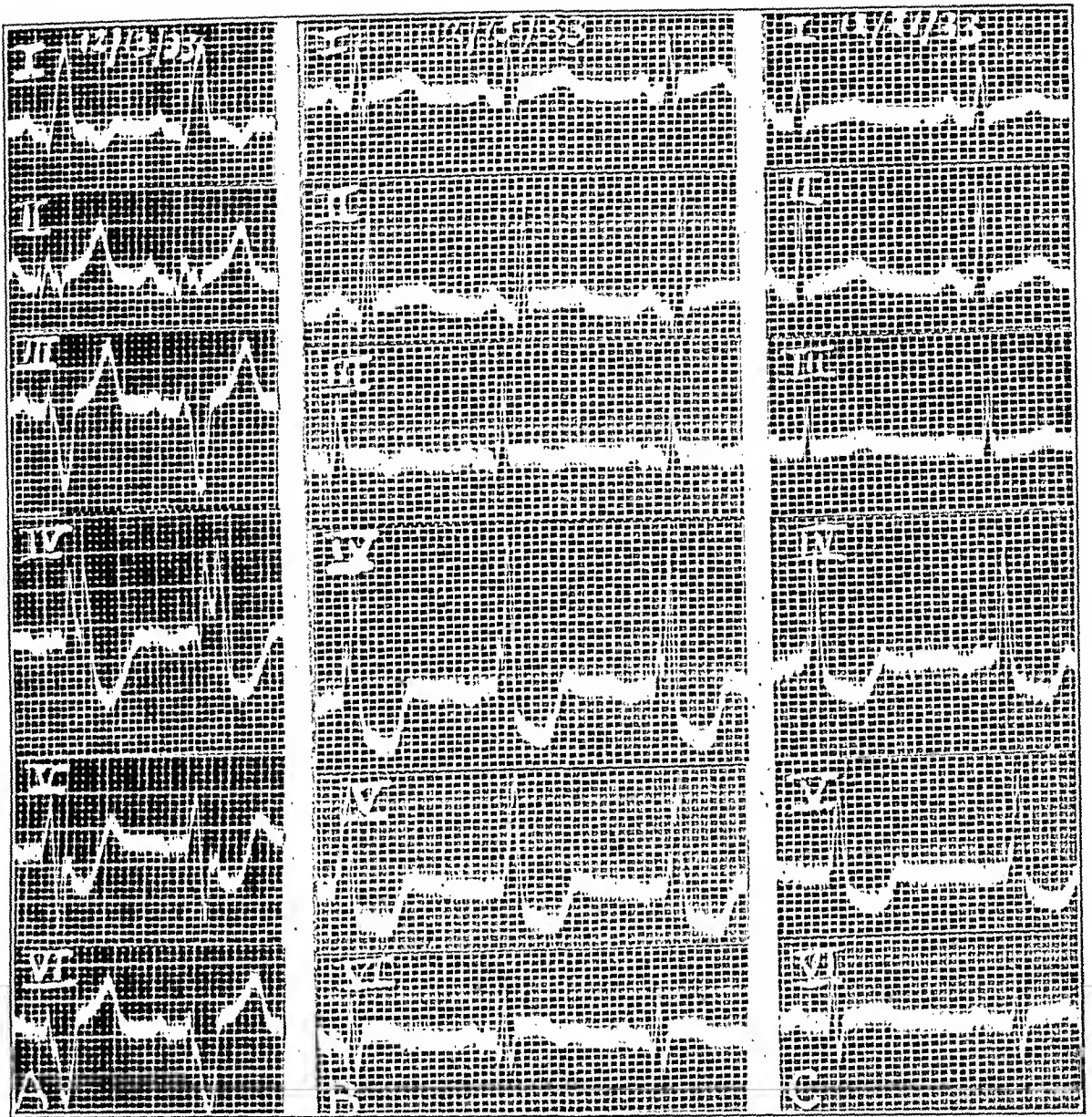


Fig. 1 (case 1).—There was an attack of coronary occlusion on December 11. The leads are numbered I to VI as in a previous publication.² The electrode from the anterior wall of the chest was placed over the apex impulse. *A* is the tracing taken on December 13, showing left bundle branch block. The RS-T interval is depressed in leads IV and V. *B* is the tracing taken on December 15. The bundle branch block has disappeared. Lead I shows a slight elevation of the RS-T interval. In lead II the elevation is more marked. In lead III it is very small. Lead IV shows an absence of the initial downward deflection of the QRS complex. The RS-T interval is depressed. Lead V is similar except that the RS-T interval is less deeply depressed. Lead VI shows a slight elevation of the RS-T interval. *C* is the tracing taken on December 21. Leads I, II and III are practically normal. Leads IV and V still show evidence of acute anterior infarction. Leads IV and V, taken with the electrode for the anterior wall on the third interspace on the left near the sternum (not reproduced here), show a much more marked deviation of the RS-T interval. Necropsy, on December 26, showed acute anteroposterior and septal infarction.

DECEMBER—*Continued*

	PAGE
Tularemia: Report of Three Fatal Cases with Autopsies. Alan Bernstein, M.D., Baltimore.....	1117
Acute, Subacute and Chronic Isolated Myocarditis: Report of a Case. Morris A. Simon, M.D., and Sidney Wolpaw, M.D., Cleveland.....	1136
Cancer as a Problem in Metabolism. Howard H. Beard, Ph.D., New Orleans	1143
Bacteriology of Normal and Diseased Gallbladders. Edmund Andrews, M.D., and Lucy Dell Henry, M.D., Chicago.....	1171
Pathology of the Vessels of the Pulmonary Circulation: Part V. O. Brenner, M.D., M.R.C.P., Birmingham, England.....	1189
Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction in the Dog. W. M. Fowler, M.D.; H. M. Hurevitz, M.D., and Fred M. Smith, M.D., Iowa City.....	1242
Theophylline in the Treatment of Disease of the Coronary Arteries. Fred M. Smith, M.D., Iowa City; Herbert W. Rathe, M.D., Waverly, Iowa, and W. D. Paul, M.D., Iowa City.....	1250
Carbohydrate Intolerance and Intestinal Flora: I. A Clinical Study Based on Sixty Cases. T. L. Althausen, M.D.; J. B. Gunnison, M.A.; M. S. Marshall, Ph.D., and S. J. Shipman, M.D., San Francisco.....	1263
Progress in Internal Medicine:	
Review of Neuropsychiatry. Stanley Cobb, M.D., Boston.....	1287
Book Reviews.....	1298
General Index.....	1301

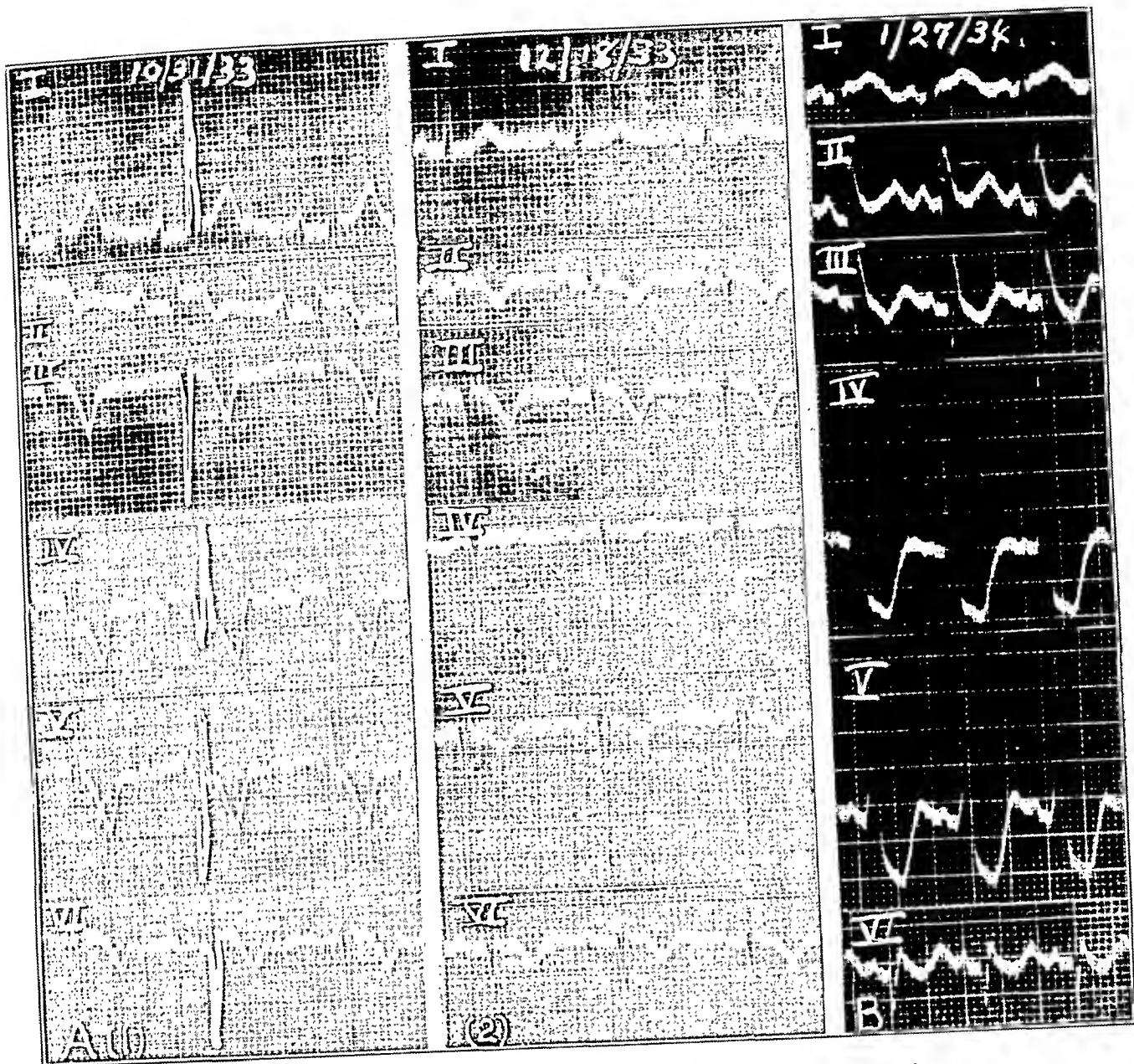


Fig. 2.—*A* shows two tracings made in case 2, in which an attack of coronary occlusion occurred on December 28. The chest leads were taken and numbered as in case 1 (fig. 1). *A1* is the tracing taken on October 31. The RS-T interval is elevated in all three limb leads, most markedly in lead II. There is a deep Q wave in lead III. Lead IV shows a preservation of the initial downward deflection of the QRS complex. The RS-T interval is depressed. Lead V is practically within normal limits. The depression of the RS-T interval is much less marked than in lead IV, and the initial downward deflection of the QRS complex is well preserved. Lead VI shows an upward deviation of the RS-T interval. *A2* is the tracing taken on December 18. It shows evidence of healed posterior infarction,² except that the T wave in lead IV is diphasic, not inverted. The signs of the anterior lesion have disappeared. Necropsy on March 7 showed evidence of a previous anteroposterior infarction, the lesion being mainly posterior. *B* shows the tracing for the patient in case 11, taken on January 27. The attack of coronary occlusion occurred on January 22 or before. Lead I shows a slight elevation of the RS-T interval. The RS-T interval in leads II and III is difficult to evaluate. Lead III shows a deep Q wave. Leads IV and V show the typical signs of acute anterior infarction. Lead VI shows a suggestion of elevation of the RS-T interval. Necropsy on January 29 showed acute anteroposterior infarction. The electrocardiographic signs in this case were suggestive but not definite enough to permit the diagnosis of the posteriorly situated part of the acute lesion.

BIOLOGIC EFFECTS OF THYMUS EXTRACT (HANSON)

ACCRUING ACCELERATION IN GROWTH AND DEVELOPMENT IN FIVE
SUCCESSIVE GENERATIONS OF RATS UNDER CONTINUOUS
TREATMENT WITH THYMUS EXTRACT

L. G. ROWNTREE, M.D.

J. H. CLARK, M.D.

PHILADELPHIA

AND

A. M. HANSON, M.D.

FARIBAULT, MINN.

WITH THE TECHNICAL ASSISTANCE OF

ARTHUR STEINBERG, B.S.

PHILADELPHIA

In this investigation we believe that we have learned something suggestive concerning the thymus gland, and, what is equally important perhaps, we have evolved a novel procedure for the study of this and possibly other endocrine organs. Following the continuous administration of thymus extract to successive generations of rats, marked acceleration in the rate of growth and development has been observed during the early life of the offspring, particularly of the third and later generations. Thus the rate of development encountered in the fifth generation of young rats born of four generations of forbears treated with a thymus extract is almost beyond belief.

METHODS OF EXPERIMENTAL PROCEDURE

A colony of 12 white rats was obtained from the Wistar Institute of June 16, 1933. These animals were divided into test and control groups. Up to the time of writing (April 16, 1934) the test animals have received by intraperitoneal injection 1 cc. of thymus extract (Hanson) daily, even during the periods of pregnancy and lactation. Litter mates born to these rats were mated in pairs, when available, and these rats have likewise received intraperitoneal injections of thymus extract, before puberty or after they reached maturity. For convenience, the animals treated before puberty will be designated as the "prepubertal" group, and those treated after maturity, as the "mature" group. "Mature control" designates the

From the Philadelphia Institute for Medical Research (Samuel Bell Jr. Laboratory) in the Philadelphia General Hospital, the Laboratories of the Philadelphia General Hospital and the Hanson Research Laboratory, Faribault, Minn.

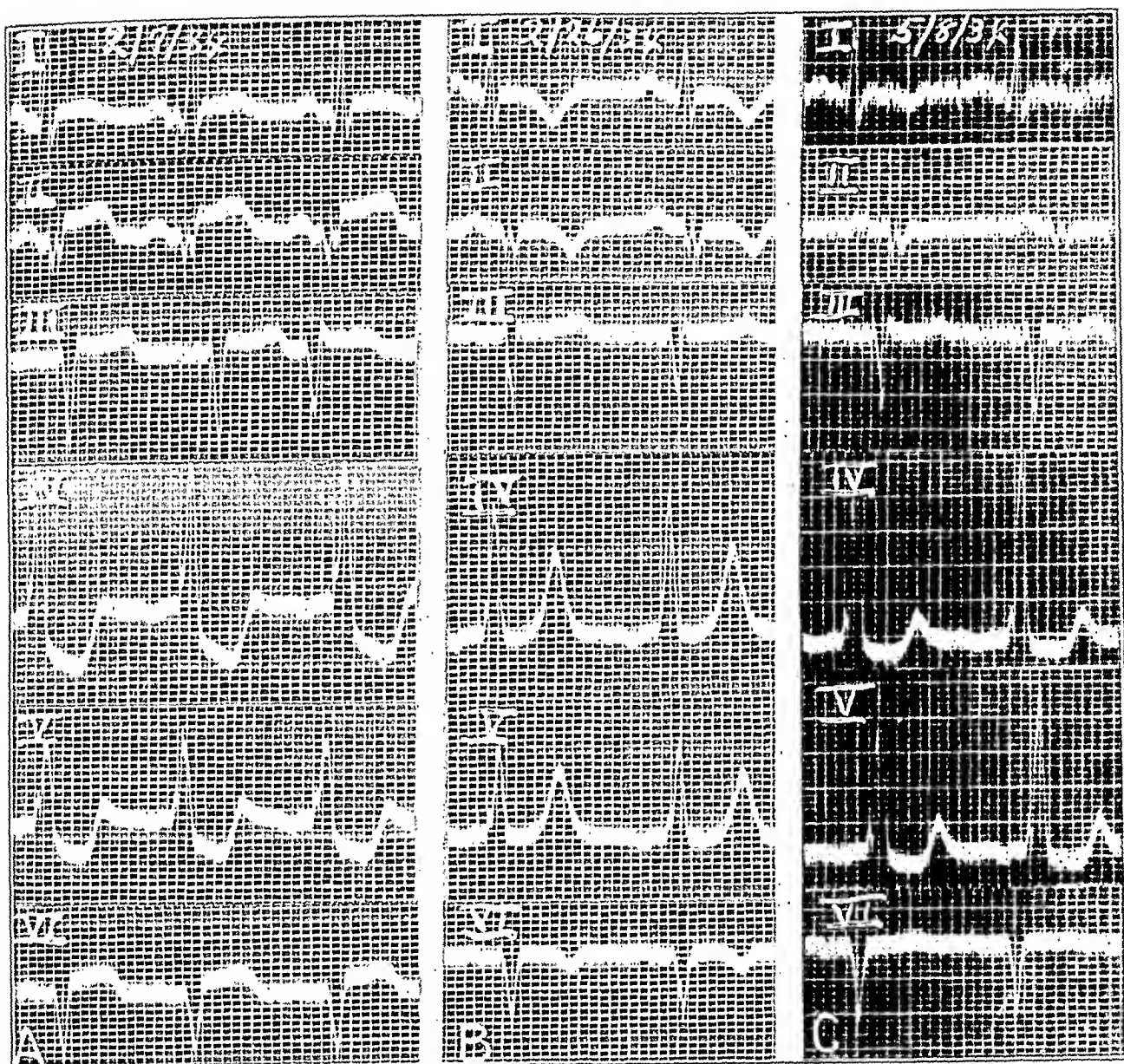


Fig. 3 (case 5).—An attack of coronary occlusion occurred on February 5. The chest leads were taken and numbered as in case 1 (fig. 1). *A* is the tracing taken on February 7. Leads I, II and III show elevations of the RS-T interval. Lead II shows a much more marked elevation than either lead I or lead III. Lead II shows a "W" wave (Edeiken, J., and Wolferth, C. C.: The Clinical Significance of the M and W Shaped QRS Complex in Lead II of the Electrocardiogram, *Am. J. M. Sc.*, to be published). Leads IV and V show the signs of acute anterior infarction, but lead V shows a smaller depression of the RS-T interval. Lead VI shows an upward deviation of the RS-T interval. *B* is the tracing taken on February 26. Leads I and II show a deeply inverted T wave. Lead IV shows a T wave 12 mm. in height. *C* is a tracing taken on May 8. The signs of healed anterior infarction² are evident.

pair corresponding to a mature test pair; "prepubertal control," the pair corresponding to a pair treated before puberty. The rats of each succeeding generation have been so treated, and the effects on the parents and on the offspring have been noted. Thus the original test animals of the first generation (F_0) have received continuous treatment since June 16, 1933; the F_1 generation, since Sept. 10, 1933; the F_2 generation, since Sept. 25, 1933;¹ the F_3 generation, since Jan. 19, 1934, and the F_4 generation, since April 15, 1934. Treatment of the young has usually been begun from the sixteenth to the twentieth day after birth in the prepubertal group and from the fortieth to the sixtieth day in the mature group. Numerous controls have been employed. At the time of writing (April 16, 1934), the fifth generation² of thymus-treated rats had been reached and we had between 300 and 400 rats in our colony.

The rats are confined in pairs in circular mesh wire cages, the floor of which is covered with excelsior. Cups for food and water are attached to the wall of each cage. All the rats used have been given a diet containing the following ingredients (parts per 100 parts): rolled oats, 15; hominy, 60; dried meat scraps, 14; dryco, 10, and sodium chloride, 1. To each 100 Gm. is added 1.25 cc.³ of cod liver oil. Additional nutriment consists of diluted milk daily and greens twice a week. After a time orange juice was added to the diet at the suggestion of Dr. H. H. Donaldson. The quantity of food is not fixed. The rats are given daily rations more than ample for their needs, and the food remaining at the end of twenty-four hours is discarded. Water is ingested *ad libitum*.

The 12 rats originally used were of Wistar strain and of known age and parentage. Eight of these were divided into mature and prepubertal test and corresponding control pairs, each pair consisting of litter mates. The remaining four mature animals were segregated according to sex. One male and one female were given injections, and the others were used as controls until they were mated after ten months.

Up to April 16, 1934, over a period of ten months, we have followed two pairs of thymus-treated rats in the F_0 generation for ten and six months, respectively. From their offspring, test and control pairs have been mated, and the same procedure has been followed in each succeeding generation. Our experiments can be divided into three groups: (1) those pertaining to continuous treatment, with daily intraperitoneal injections in succeeding generations; (2) those in which treatment (daily injections) was interrupted for one or more generations, and (3) feeding experiments in which the thymus extract was administered by mouth. In group 1 three series of animals were studied: 1A, the original rats given injections of thymus extract (Hanson) since June 16, 1933; 1B, a series of rats subjected to identical treatment (started on Oct. 5, 1933), to act as a control for the first series, and 1C, a series of rats subjected to similar treatment with a new preparation of thymus extract (Hanson) obtained from another source.

From our original colony of rats, 1A, which have received injections of thymus extract (Hanson) since June 16, 1933, 17 litters were born, and from these 7 control and 10 test pairs were mated in the F_1 generation; 23 litters, 9 control and 14 test pairs, in the F_2 generation, and 13 litters, 4 control and 9 test pairs, in the F_3 generation. From this it is apparent that control pairs have been provided for each generation under treatment.

1. The parents were treated only one day prior to delivery; the offspring, on the fifteenth day of life.

2. In the text, F_0 animals are referred to as first generation and F_4 as fifth generation, respectively.

3. Gottesman, J., and Jaffe, H. L.: *J. Exper. Med.* **42**:413, 1925.

studied with chest and limb leads, the electrocardiograms showed the signs of this lesion. In 2 of the 20 cases which came to necropsy, we observed this lesion (cases 1 and 11). One showed evidence suggesting a previous acute anteroposterior lesion (case 2).

The cause of the extension of an acute infarct from the anterior to the posterior surface of the left ventricle, or vice versa, would seem to be an anatomic or pathologic variation in the coronary arteries. Consequently one might expect that a patient who had had an infarct in one surface of the heart and who subsequently had a similar lesion in the other would usually show signs of the acute anteroposterior lesion with the second attack. However, this is not necessarily the case. None of the 3 patients in this group who came to necropsy showed a previous infarction of the side opposite the main lesion. Moreover, in 4 other cases of acute cardiac infarction there was no electrocardiographic evidence of an acute anteroposterior lesion, although necropsy in each case showed an acute infarct of one wall of the left ventricle and a healed lesion of the opposite side.

Six of the 10 patients whose cases are reviewed in table 1 have died. Prognostic figures expressed in percentage have little significance in such a small group of cases. However, it would seem that the prognosis of this type of lesion is probably not much more unfavorable than that of the typical infarct of the anterior wall.¹

SUMMARY

A group of 10 cases is reported in which the electrocardiographic evidence pointed to recent infarction of both the anterior and the posterior wall of the left ventricle. Permission for necropsy was obtained in 2 of the cases. In each instance an infarct was found involving the lower part of the anterior wall, the apex and the lower part of the posterior wall.

The electrocardiographic findings were as characteristic as those of recent infarction limited to the anterior or the posterior wall.

The recognition of the signs of acute involvement of both the anterior and the posterior wall removes a source of confusion in the electrocardiographic localization of myocardial infarction.

Dr. A. I. Rubenstone and Dr. E. S. Dillon gave us permission to report the cases of patients who were under their care.

Of the straight control animals, 2 pairs of rats yielded 9 litters in the F_1 generation. From these, 2 mated pairs yielded 12 litters in the F_2 generation. No further matings have been made.

NATURE OF THE THYMUS EXTRACT USED

The extract used in these experiments was prepared by Hanson⁴ in 1930. The method and nature, briefly, were as follows:

The thymus glands of from 2 to 6 week old calves were extracted in a 0.5 per cent solution of hydrochloric acid with heat. This method of extraction differs from Hanson's method of extracting the parathyroids simply in the degree of acidity used. The thymus extract thus prepared is extremely stable and is entirely potent and satisfactory for injection into rats even after being kept at room temperature for from two and a half to four years. The extract is golden yellow; its taste and smell resembled those of bouillon. It has a p_H of about 5 and is nontoxic in relatively large doses and nonirritating locally on injection.

Chemical analysis of this extract made after three years yielded the following values:

	Mg. per 100 Cc.
Total nitrogen (micro-Kjeldahl method).....	5.75
Calcium	4.00
Inorganic phosphorus.....	12.80
Lipoid phosphorus.....	19.00
Sodium chloride.....	365.00
Cholesterol	10.00
Uric acid.....	14.00
Reduced and oxidized sulphur compounds calculated as glutathione.....	15.8

The strength of the extract used represented 0.6 Gm. of raw calf thymus per cubic centimeter.

BIOLOGIC DATA ON NORMAL AND ON CONTROL RATS

As our test animals evidence precocity, it is essential to keep in mind the normal biologic data as revealed in control animals. Our control data are of several kinds: 1. The data obtained in the study of rats at the Wistar Institute as summarized by Donaldson⁵ in his book on "The Rat." 2. Observations on normal controls, 6 Wistar rats (litter mates of corresponding thymus-treated rats) and their descendants, paired and raised in our laboratory on the same food and under the same conditions as the thymus-treated test rats. These control animals received injections of a saline solution of glycerin over a period of months. 3. Observations on special controls, rats born of thymus-treated animals, which were used as controls for each generation. These controls are described later in a special section devoted to interruption of treatment. 4. Observations on a small group of animals on which treatment with an extract of the lymphatic glands is just being started.

4. Hanson, A. M.: Treatment of Cancer with Thymus Extract, J. A. M. A. 94:653 (March 1) 1930.

5. Donaldson, H. H.: The Rat, ed. 2, Philadelphia, Wistar Institute of Anatomy and Biology, 1924.

the motility of isolated segments of the stomach and intestines. Plant,⁸ using dogs with gastric and intestinal fistulas, reported that spirit of spearmint brought into the intestinal loop increases its tone and contractions. Later, Plant and Miller⁹ published reports of experiments on segments and strips of intestine in vitro. Small doses of peppermint increase their motility and tone; larger amounts inhibit it. Stross¹⁰ reported that menthol inhibits motility and depresses and abolishes the tonus of isolated pieces of intestine. Arnold¹¹ noted a paralyzing action of peppermint on the stomach and a stimulating action on the intestine. Sommerfield, Kuenzel and Todd¹² observed with the fluoroscope that peppermint increases the amplitude and vigor of the contractions of the stomach. Heupke and Hollaender,² who made an extensive study of the gastric secretory response to many spices and volatile carminative oils, reported that oil of peppermint has no influence on the secretion of hydrochloric acid by the stomach. This is the only paper we have been able to find in the literature which deals with the direct influence of oil of peppermint on gastric secretion. These authors assumed that the beneficial effect of oil of peppermint in epigastric distress is produced by anesthesia of the mucosa of the stomach. One more paper must be mentioned, although it deals with the effect of oil of peppermint on the secretion of bile. Heinz¹³ stated that oil of peppermint has a marked cholagogue effect in frogs, rabbits and cats. He also reported good clinical results of its use in man because of this cholagogue action.

We have made the observation on ourselves that the chewing of peppermint candy or lozenges relieves pain caused by hunger and distress after a heavy meal. Tea made from the dried leaves of peppermint is often used by the peasants in France and Germany to relieve abdominal cramps. Much is written in textbooks of pharmacology about an anesthetizing action of oil of peppermint and of menthol on the mucous membranes.

TESTS AND OBSERVATIONS

Effect of Oil of Peppermint on the Secretions of the Stomach During Fasting.—Eleven tests were carried out on nine patients in the fasting state. A Rehfuß tube was introduced into the stomach, and ten minute samples were aspirated. From two to five control samples were taken, and then from 1 to 2 cc. of oil of peppermint (the U. S. P. preparation was used throughout) with 10 cc. of a

8. Plant, O. H.: J. Pharmacol. & Exper. Therap. **16**:311, 1921.

9. Plant, O. H., and Miller, G. H.: J. Pharmacol. & Exper. Therap. **27**:149, 1926.

10. Stross: Arch. f. exper. Path. u. Pharmacol. **95**:5, 1922.

11. Arnold, W.: Monatschr. f. Kinderh. **30**:225, 1925.

12. Sommerfield, W. A.; Kuenzel, W. M., and Todd, T. W.: J. Lab. & Clin. Med. **17**:151, 1931.

13. Heinz: Therap. Halbmonatsh. **34**:356, 1920.

In his book on "The Rat" Donaldson gave the following data as the average norms for the rate of development:

Ears open.....	2½-3½ days
Incisors erupt.....	8-10 days
Eyes open.....	14-17 days
Hair obscures genitalia.....	16 days
Testes descend.....	40 days
Vagina open.....	72 days
Menopause occurs.....	15-18 months

The average norms for our control rats approximate Donaldson's figures closely, as shown in table 1. The chief difference lies in the earlier gonadal development.

TABLE 1.—*Comparison of Our Control Rats with Those of the Wistar Institute*

Strain	Number in Litter	Days						Comment
		Opening of Ears	Eruption of Teeth	Appear- ance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	
Wistar Institute	6.1	2½-3½	8-10	16	14-17	40	72	Fed a varied breeders' diet
Philadelphia In- stitute for Medi- cal Research*	5.0	2½-3	9-10	12-16	14-17	31-40	55.62	Fed an adequate stock diet

* The figures are based on observation of 104 animals.

Biologic data relative to the rats constituting the normal control series from the second generation are given in table 2. The largest number of litters born was 7 in seven months (F_0). The average interval between gestations was thirty-seven days. The average number of offspring in 21 litters was 4.9. The average weight at birth was 4.6 Gm. per litter. The ears opened, the incisors erupted and the eyes opened at the normal time. Hair appeared between the twelfth and the sixteenth day in all the animals except two, in which it appeared between the eighth or ninth and the fifteenth day. The testes descended between the thirty-fifth and the fortieth day except in two animals, and the vagina opened between the fifty-fifth and the sixty-second day. The mortality among our control animals was very high, many of them being destroyed by the parents, eaten or neglected. The number of control animals in the first generation that survived was 9 of 33, and in the second generation, 30 of 70.

RESULTS OF CONTINUOUS TREATMENT OF SUCCESSIVE GENERATIONS OF RATS BY DAILY INTRAPERITONEAL INJECTION OF 1 CC. OF THYMUS EXTRACT—SERIES 1 A

Data Relating to the Growth and Development of Test Rats of the First Generation (F_0) and Their Controls.—In the segregated group, the male test animal became somewhat heavier than the control, the

on the pituitary gland in *The Journal of the American Medical Association*), but in 1932 Houssay, Mazzocco and Biasotti added one important point, namely, that this resting condition of the gland was accompanied by an increase in the concentration of iodine of the gland.

Byars, Friedman, Siebert and Loeb (1932) showed that there was no variation in the activity of extract of the anterior lobe of the pituitary gland from cattle depending on the season of the year in which the glands were obtained. Houssay, Novelli and Sammartino (1932) found no change in the effectiveness of the extract even if the thyroid glands of the animals had been removed as long as a month and a half before the pituitary gland was obtained.

The experiments of Marine and his associates²⁴² are very interesting in that these investigators were able to produce exophthalmos in a few thyroidless guinea-pigs by the administration of extract of the anterior lobe, and also in rabbits by the administration of cyanide. Friedgood also showed that exophthalmos from the administration of extract of the anterior lobe often gradually became more pronounced after the return of heat production to or below normal. They were of the opinion that these experiments indicate that there is some underlying similarity in the response of the thyroid produced either by extract of the anterior lobe or by cyanide; they suggested that this similarity indicates thyroid deficiency in both instances.

In 1933 Anderson and Collip⁷ announced the preparation of a highly purified extract of the anterior lobe of the pituitary gland and confirmed the physiologic effects noted previously by the less highly purified extracts; their preparation gave complete replacement therapy and produced hyperplasia of the thyroid together with hyperthyroidism in hypophysectomized rats and dogs.

P. E. Smith³¹⁶ (1932 and 1933) noted that in hypophysectomized, thyroparathyroidectomized rats, skeletal growth was distinctly greater when thyroid extract was given together with extract of the anterior lobe of the pituitary gland than when extract of the anterior lobe was given alone; on account of this apparent synergistic action he suggested that both extracts be used in the clinical treatment of pituitary dwarfs.

Schneider and Widmann³⁰⁸ (1932) presented evidence which they interpreted as indicating that the beneficial effect of iodine as a pre-operative procedure is not explainable on the basis of a direct action of iodine on the thyroid-stimulating hormone. Grab (1933) not only showed that there was a decrease in colloid following the administration of extract of the anterior lobe but that, in addition, the concentration of both thyroxine and di-iodotyrosine in the colloid was decreased. Loeser found by the use of certain extracts of the anterior lobe that in addition to hypertrophy of the thyroid gland there was in some instances hypertrophy of the adrenal gland. The adrenal hypertrophy did not develop

TABLE 2.—Rate of Development of Albino Rats in the Control Series (Not Treated)

Parents (No.) [*] 18 and 19 P P C	Period Between Gesta- tions, Days	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Opening of Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Preg- nancy (Days from Birth)	Casting First Litter (Days from Birth)	Comment
40 and 41 P P C	89	8/30/33	7	4.8	4	3	9-10	12-14	16	36	55	9/23/33	70	91	
	27	11/27/33	3	4.5	0	Neglected
	46	12/24/33	7	4.3	2	2.5	10	Both males
	24	2/10/34	5	5.0	0	3	10	14-16	16	36	60	Died at 24 days
	24	3/ 6/34	2	5.2	0	3	10	12-17	17	Eaten at 1 day
22 and 23 M C	..	3/30/34	12	Head of 1 animal found
	20	11/29/33	8	4.2	0	Unfed
	21	12/18/33	9	4.6	0	Unfed
	22	1/ 8/34	7	4.6	0	Unfed
	49	1/30/34	8	4.3	7	3	9	8-15	15	38	62	2/26/34	Have not bred
48 and 49 M C	..	3/24/34	4	5.0	4
	..	7/ 9/33	3	5.6	3	3	9	9-15	15	40	55	8/20/33	55	75	..
	134	11/18/33	2	3.0	0
	25	12/13/33	3
	..	9/12/33	1	4.1	0	Died on following day
25 and 27	47	10/26/33	6	3.9	0	Died; crushed
	38	12/ 3/33	5	4.1	0	Died; unfed
	34	1/ 6/34	6	5.0	5	3	9-10
	31	2/ 6/34	7	4.7	6	2 1/2	12-15	14-15	36	Died; devoured
	28	3/ 4/34	4	4.9	3	3	10	15-16	35	Died; unfed
..	47	4/10/34	5	6.4	5	3	10	12-15	33	55	All males
	12-14	16	31	Not opened	All males
	Unmated
	To be mated

* The letters P P C indicate prepubertal control; M C, mature control.

a great deal of importance in cases of disease. In Harrison's case ¹²⁹ of congenital pulmonary stenosis with a patent interventricular septum the bronchial arteries were greatly dilated, and it was possible that much of the blood aerated in the lungs was carried by the bronchial arteries. Mallory and Means ²⁰⁰ in their case of thrombosis of the right pulmonary artery observed greatly enlarged bronchial arteries running to the right lung. Schlaepfer ²⁶⁸ found that three months after the ligation of a pulmonary artery in the dog the diameter of the bronchial arteries to the corresponding lung may be increased fourfold. In such cases, however, as in the cases of Hart ¹³⁰ and Stadelmann, ²⁸² in which either the stem or both main branches of the pulmonary artery were almost or entirely occluded by thrombi and in which the authors assumed, without demonstrating, an increased circulation through the bronchial arteries, it is probable that the increased bronchial circulation maintains the nutrition of the lung and prevents infarction, but it is not likely that the bronchial arteries serve any important respiratory function. In such cases only blood which has already passed through the lungs and is therefore already oxygenated flows through the bronchial arteries, and it can undergo little if any further oxygenation in the lungs. It seems that the respiratory function of the bronchial arteries can be of importance only in cases, such as Harrison's, in which a congenital abnormality allows blood from the right side of the heart to enter the left side without first passing through the lungs, so that the blood which flows through the bronchial arteries is partly unoxygenated.

Communications between the pulmonary and the systemic veins other than the bronchial have also been described. Schlaepfer ²⁶⁷ showed that after experimental obstruction of the pulmonary veins, if pleural adhesions were present, veins from the surface of the lung ran out along the adhesions to communicate with tributaries of the superior vena cava, thus somewhat relieving the pressure in the pulmonary circulation by shunting some of the blood into the systemic circulation. Some clinical importance has been attached to such anastomoses. Trunicek ²⁹⁹ described dilatation of the veins over the front of the chest and abdomen as a characteristic sign of increase in pressure in the pulmonary circulation and stated that if these communications are well marked, emphysema may exist without hypertrophy of the right ventricle. (This seems an inadequate explanation of the frequent absence of right ventricular hypertrophy in cases of emphysema, since any obstruction to the pulmonary circulation is presumably in the pulmonary capillaries, and the pressure in the pulmonary veins might be expected to be even less than normal.) Achard ² and Rogers ²⁵⁴ also mentioned dilatation of the veins over the chest in some of their cases, and in one of the cases in the present series the dilatation was so marked as to lead to an erroneous diagnosis of pressure on the superior vena cava.

female becoming heavier after mating. In the mated groups no constant effect on the animals' weight was noted. However, as shown in table 3, the test animals seemed to breed more frequently and to have larger litters, the average weight of the young being higher. Thus the mature test pair (rats 20 and 21) cast 9 litters of 78 animals, and the mature control pair (rats 22 and 23) cast 3 litters of 8 animals from July 10, 1933 to March 13, 1934, a period of eight months, at which time the control mother died.⁶ The prepubertal test pair (rats 16 and 17) cast 4 litters of 27 animals, the female dying during labor on Nov. 17, 1933, while the corresponding control pair (rats 18 and 19) cast 2 litters of 10 animals for a corresponding period of two months, from Aug. 30 to Nov. 27, 1933.

These figures for the test and control parents should not be regarded as accurately representative. The mature control pair were apparently not good breeders. Table 2 reveals corresponding data on the other untreated animals. The table shows that 1 pair (rats 18 and 19) cast 6 litters of 24 animals and a second pair (rats 48 and 49) cast 7 litters of 34 animals. The average litter, however, contained in each instance less than 5 young, whereas the litters born to the original test animals comprised on an average 7 and 7.8 animals. Only 1 pair of untreated rats had an average of 7 young per litter.

Data Relating to the Growth and Development of Rats of the Second Generation (F_1).—In all 124 rats were born in 17 litters to 4 pairs of test animals of the first generation (F_0) under treatment. The biologic data for this group of animals are summarized in table 3.

Interval Between Gestations: Because of the death of 2 mothers only 1 pair has continued to breed up to the time of writing, having cast 9 litters in eight months. The dates of birth reveal rapid breeding. Thus for the prepubertal test pair (rats 16 and 17) the longest period between births of litters was twenty-seven days and the shortest twenty days. For the mature test pair (rats 20 and 21) the shortest period was twenty-three days, and in 5 instances it was thirty days or less. In the last pair (rats 38 and 39), the intervals were twenty-four and twenty-two days, respectively. The average period between births for the second generation group as a whole was twenty-seven and nine-tenths days.

Size of Litters: The average number of rats to the litter was 7 for the first pair, 8.6 for the second and 6.3 for the fourth, a total of 124 animals for 17 litters or more than 7.3 rats per litter. The third pair had only 1 litter, the number of which was undetermined. Perhaps the contrast between the size of the litters early and late in the fertile period is of significance. Thus for the first 7 pregnancies (rats 20

6. Tables 2 and 3 show the length of the period covered.

Gieson's, blue with Mallory's phosphotungstic hematoxylin and red with Mallory's connective tissue stain. The length of the annulus from the point of attachment of the cusp to the beginning of the elastic tissue and muscle of the media of the pulmonary artery varies from 0 to 6 mm. The nearer the commissure of the cusps the section is taken the less is the extent of the annulus. Usually but not always the lower half or three-fourths of the annulus is backed by heart muscle. Away from the commissures the muscle and the elastic tissue of the pulmonary artery end in a wedge the downwardly directed apex of which is subintimal. The fibrous tissue of the annulus is external to the wedge until it becomes continuous with the media and with the dense inner layer of the adventitia of the pulmonary artery. In the region of the commissures of the valve the arrangement is similar, except that the apex of the wedge of medial muscle and elastic tissue is situated immediately beneath the adventitia and there it often extends down to, or sometimes below, the root of the cusp, the fibrous tissue of the annulus being continued up on its internal aspect.

In their description of the insertion of the aorta into the ventricle (and they stated that the same description, with minor exceptions, applies to the pulmonary artery) Gross and Kugel said that the elastic fibers of the intima unite into one or more layers which sweep around the "sinus pocket" and ascend as a delicate elastic layer beneath the endothelium of that aspect of the cusp directed toward the arterial wall (the "arterialis" of the valve). This description must be somewhat modified in the case of the pulmonary artery. In the normal pulmonary artery practically the only intimal elastic tissue is the internal elastic lamina. Below the apex of the medial wedge it rapidly thins and becomes delicate. Occasionally it is continued down around the root of the cusp and into its arterialis, as described by Gross for the aorta; but, more often, just below the apex of the wedge, the lamina disappears and is replaced by a single row of delicate, fairly closely packed, circularly directed elastic fibrils, which appear as a row of dots in longitudinal section. Often these disappear before the root of the cusp is reached, and there then may be no elastic tissue in the arterialis of the cusp. Sometimes the fibers continue into the cusp, where they again become continuous.

In the annulus there is no muscle, and the only elastic tissue is represented by the few delicate fibrils lying immediately beneath the endothelium. Aortic aneurysm is usually ascribed to the destruction of the medial muscle and elastic tissue and its replacement by stretchable fibrous tissue. However, this is the normal arrangement at the root of the pulmonary artery and of the aorta, even though the area involved is small and is usually backed in its lower part by heart muscle. If the usual explanation of the origin of aneurysms is correct, it is difficult to understand why small-mouthed saccular aneurysms are not normally present at the roots of the aorta and pulmonary artery.

TABLE 3.—*Rate of Development of Treated Albino Rats in the Second Generation (F₂)*

Parents (No.)*	Period Between Gesta- tions, Days	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Appearance of Teeth	Opening of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Preg- nancy (Days from Birth)	Casting of First Litter (Days from Birth)	Comment
16 and 17 P P T	..	8/30/33	9	4.3	5	2	7	10-14	14	29	30	9/23/33	98	106	
	22	9/21/33	6	4.5	6	2	5	10-12	14	29	30	10/ 5/33	21	42	
	27	10/18/33	4	...	0	
	20	11/17/33	8	5.7	
20 and 21 M T	..	7/10/33	11	5.0	9	2	9	8-10	
	24	8/ 3/33	8	4.9	7	2-2½	8	7-8	14	29	35	8/20/33	Litter devoured
	30	9/ 2/33	9	6.1	8	2	6	7-10	14	28	35	10/ 5/33	40	..	Female died in labor
	23	9/29/33	5	4.4	4	2	6	6-8	12	21	32	12/19/33	69	89	
	27	10/22/33	11	4.3	11	2	6	3-5	13	22	35	12/19/33	
	51	1/ 8/34	15	6.0	7	1	1	4-6	14	22	42	10/22/33	140	162	
	36	2/14/34	12	6.1	8	1	2	4-6	13	21	32	2/ 2/34	70	92	
	27	3/13/34	3	5.0	0	30	1/31/34	68	89	
	40	4/23/34	4	6.0	0	65	86	
38 and 39 M T	..	12/20/34	3	5.2	3	2	2	6-10	10	12	
	24	1/13/34	8	4.3	0	
	22	2/ 4/34	8	5.0	7	1-2	1-2	7-8	14	21	
			5.0	0	

* The letters P P T indicate treated before puberty; M T, treated after maturity.

* The letters P P T indicate treated before puberty; M T, treated after maturity.

homogeneous matrix which stains a paler pink. In a large mass of fibrous tissue there may sometimes be found isolated muscle cells and short elastic fibrils. A few of the fibrous patches are often looser and more fibrillar and contain a few mononuclear cells.

Fairly large twigs from the adventitial vasa vasorum penetrate into the outermost part of the media, the various medial layers in the neighborhood being arranged concentric to the vessel. Capillaries are present in the outer half or two thirds of the media.

In old age the irregularity of the arrangement of the media is often increased and there is often an increase of the connective tissue, which is formed into large masses at the expense of the elastic tissue and muscle. It seems probable that such large masses of connective tissue have in the past been mistaken by some authors for syphilitic scars. The adventitia consists of fibrofatty tissue. Usually the layer next to the media consists of dense fibrous tissue, while the rest may be mainly fatty. There are many irregular short elastic fibers and sometimes a few small bundles of longitudinal muscle. The line of demarcation from the media is often not sharply marked. Many blood vessels and nerves are present.

Large Branches.—The structure of the branches remains essentially the same from the main right and left pulmonary arteries down to the intrapulmonary branches of about 1 mm. in outside diameter (excluding the thickness of the adventitia, which it is often difficult to demarcate from the surrounding fibrous tissue). In children the same structure is seen in arteries that are even smaller. The intima consists of endothelium lying directly on a thick internal elastic lamina. In some cases that are not otherwise abnormal a thin layer of connective tissue intervenes either in patches or over the whole circumference. This, though common, is probably pathologic. The thickness of the media varies with the size of the vessel, but it ranges from 5 to 15 per cent (average, 9.8 per cent) of the external diameter of the artery exclusive of the adventitia. This is undoubtedly too large for the arteries during life, since then the lumen would be distended. Moreover, the figures are probably not strictly comparable among themselves, since the degree of postmortem contraction probably varies. Therefore, only wide departures from the "normal" range should be accepted as pathologic. The media consists of elastic laminae which are more regular than in the stem, their number depending on the size of the artery and ranging from three or four in arteries of 1 mm. external diameter, to from sixteen to twenty in arteries 5 or 6 mm. in diameter. They are long (sometimes traceable completely around the circumference of the artery), so that fenestrations are smaller and less frequent; fairly regular in thickness, and fairly parallel, though with frequent anastomoses. Muscle is relatively more abundant than in the stem, and almost all of

and 21) the average number of offspring per litter was 9.5 while for the last 3 pregnancies it was 4 or less.

Weight at Birth: The average birth weight per litter was 4.8 Gm. for the young of the prepubertal group (7 litters of 46 animals) and 5.3 for the offspring of the mature group (10 litters of 78 animals). This gave a combined average birth weight of 5.1 Gm. per litter.

Survival of Offspring: Of the 124 offspring in the second generation, 73 (58 per cent) survived. In the test series 16 or more young rats succumbed owing to the mother's death during parturition. The best rate of survival was encountered in the first 7 litters of the mature test animals, 54 out of 71 (76 per cent) young surviving; but only 3 of the 11 animals in the following three litters survived.

Opening of Ears: According to Donaldson, the ears open normally at between $2\frac{1}{2}$ and $3\frac{1}{2}$ days of age, but there is a cellular plug in the meatus which may persist for some time longer. According to Wada,⁷ rats can hear at from 9 to 12 days of age. The earlier date is exceptional. Lane⁸ regarded 12 days as the earliest age at which he obtained an auditory response.

At birth the external ear appears merely as a nubble or small mass raised above the surface of the skin. Normally a few days after birth a free margin becomes detached which becomes the lobule or external ear. This development is referred to as the opening of the ear. Thus in our second generation test rats the ear opened in two days in all the litters except the sixth and seventh, in which the ears opened on the first day.

Eruption in Incisors: In rats the incisors are the first teeth to appear, eruption occurring at from 8 to 10 days of age. In our prepubertal animals this phenomenon occurred at the age of 7 days in the first litter and of 5 days in the second. The dates of the eruption of teeth in the 9 litters of one mature pair indicated that eruption of the incisors occurred in the first litter at 9 days, in the third, fourth and fifth litters at 6 days and in the sixth and seventh litters at from 1 to 2 days. Thus the eruption of incisors is increasingly accelerated in succeeding litters born to thymus-treated animals. Prolonged treatment of both parents prior to their mating results in a similar precocity in the eruption of teeth.

Appearance of Fur: In the prepubertal group of the second treated generation hair obscured the genitalia as early as the tenth to the twelfth day in the second litter. In the litters born of the mature animals the body was covered between the eighth and tenth day in the first litter,

7. Wada, T.: *Anatomical and Physiological Studies on the Growth of the Inner Ear of the Albino Rat*, Mem. no. 10, Philadelphia, Wistar Institute of Anatomy and Biology, 1923.

8. Lane, H. H.: *Dissert.*, Princeton University, 1927.

Muscular Arteries.—The muscular arteries range in external diameter from 1 to 0.1 mm. or less and at their upper limit pass imperceptibly into the large elastic arteries. The intima consists of endothelium which rests directly on a well marked internal elastic lamina (fig. 3). The media is from 6 to 32 per cent of the external diameter (average, 14 per cent). The same remarks apply to these figures as to those for the large arteries. The media consists of circular muscle between internal and external elastic laminae. In all but the smallest arteries there are a few short, fine, irregular elastic fibrils. There is no connective tissue. The adventitia consists of a fairly thick layer of dense connective tissue.

Arterioles and Venules.—These are considered together because, owing to their similarity of structure, it is difficult to differentiate between them without seeing them joining an artery or a vein. There is no precise definition of the word arteriole, and many writers in their description of the pulmonary circulation use it as synonymous with the term small artery. In the systemic circulation it has been defined by various authorities as an arterial vessel with a diameter of less than 0.3 mm.,¹⁹⁷ less than 0.1 mm. or (Landis) less than 0.04 mm. Cowdry,⁶⁵ in view of these very different criteria, considered that it is not so much a question of the absolute diameter as of the relative thickness of the wall, which is greater than in any other type of vessel. It is these vessels which by the contraction and relaxation of their powerful walls regulate the blood pressure and the blood supply to the various organs. The afferent vessels of the renal glomeruli and the arterioles of the malpighian bodies in the spleen are typical examples. Measurements made in a number of cases show that these have an external diameter of from 0.023 to 0.066 mm. (average, 0.043 mm.); a lumen with a diameter of from 0.008 to 0.016 mm. or of from 18 to 50 per cent (average, 28 per cent) of the external diameter, and a muscular wall from 0.008 to 0.027 mm. thick, or from 25 to 41 per cent (average, 36 per cent) of the external diameter. Thus, after death the lumen in these vessels is about a fourth and the wall over a third of the external diameter.

There are no vessels of this type in the pulmonary circulation. The arteries down to 0.1 mm. have a media consisting of a thin layer of muscle between internal and external elastic laminae. Below 0.1 mm. (fig. 3) the wall of the vessel consists of a tube of endothelium surrounded by a single spirally wound elastic fibril, which seems to be continuous with the external elastic lamina of the parent artery. Occasionally in the larger of these arterioles the elastic fibril splits here and there to enclose single muscle cells. The walls of these vessels range in thickness from 4 to 9 per cent (average, 5.7 per cent) of the external diameter, compared with an average of 36 per cent for the systemic arterioles. Ljungdahl¹⁷⁶ and Trunicek²⁹⁹ also described a similar structure for the pulmonary arterioles, though Trunicek called them capillaries. It is dif-

only from 2 to 7 per cent (average, 4 per cent) of the external diameter. Several rather irregular elastic fibers appear instead of one fiber, and between them there are much connective tissue and a few muscle cells. The intima still consists of endothelium directly on an elastic fiber.

In the larger veins (from 1 to 5 mm. or more in diameter) the media consists of connective tissue with many fine, irregular elastic fibers and varying amounts of irregularly arranged smooth muscle. Often there is a thin layer of muscle immediately beneath the internal elastic lamina, and bundles of muscle are scattered through the rest of the media. The adventitia is usually thick, and there is no clear line of demarcation between it and the media. It contains irregular but chiefly longitudinal elastic fibers and often bundles of longitudinal muscle. There are also many vessels here.

The main (extrapulmonary) pulmonary veins show a similar structure. The intima consists of endothelium which lies directly on an elastic lamina. The media consists of connective tissue with a great deal of fine irregular elastic tissue and a varying amount of muscle. The adventitia is a thick layer of fibrofatty tissue with many vessels and some nerves. In it a tube of cardiac muscle is continued from the left auricle for varying distances along the veins, separated from the media by a zone of fibrofatty tissue.

PATHOLOGIC PHYSIOLOGY OF THE PULMONARY CIRCULATION

There is at present no method of estimating the pressure in the pulmonary artery in man, and the methods used in animals are unsatisfactory. Scarff²⁶⁶ found that the pulmonary systolic pressure in dogs was from 18 to 27 mm. and the pulse pressure was from 7 to 14 mm. of mercury. Dunn⁸⁵ found in goats that the mean right ventricular pressure for the various phases of respiration was from 9.5 to 27.5 systolic and from 1 to 11.5 diastolic. Thus the old statement that the pressure in the pulmonary artery is about one sixth of that in the aorta is confirmed for the systolic though not for the diastolic pressure. The pressure in the pulmonary veins presumably fluctuates around that in the left auricle, depending on the phases of the cardiac cycle, and the pressure in the pulmonary capillaries must be intermediate.

Other things being equal, an increased output by the right ventricle must result in an increased pressure all the way from the right ventricle to the left auricle, and Patterson and Starling²²⁸ have shown that in the heart-lung preparation, in which, however, the conditions cannot be regarded as normal, this actually occurs. The normal stimulus to an increased output of the right ventricle is an increased venous return, such as occurs in muscular exercise. It might therefore be expected that exercise would cause an increase in the pressure in the pulmonary

of the second generation were more numerous and somewhat heavier at birth. The rate of mortality in the young was less and the rate of survival greater. The rate of growth and development was but little affected in the animals of earlier litters but became accelerated in the later litters. This acceleration was accruing in character and became definitely manifested only as succeeding litters were born to thymus-treated parents. Moderate precocity was observed in the later litters of second generation rats born of thymus-treated test animals.

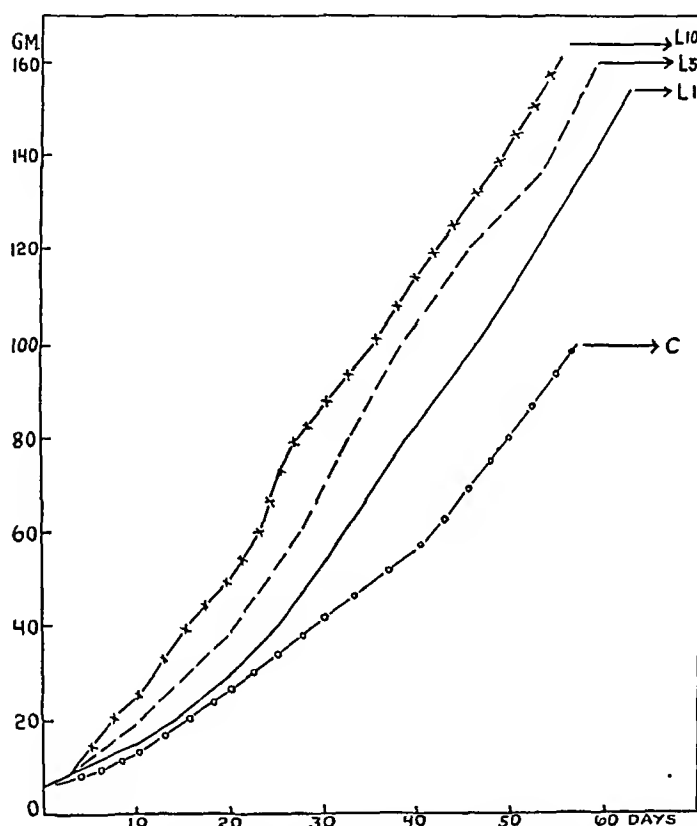


Fig. 1.—Curves showing growth of control litter and of first, fifth and tenth litters of rats 20 and 21.

*Data Concerning the Growth and Development of Rats of the Third Generation (F_2).—*In all 115 rats were born in 15 litters to 5 pairs¹⁰ of rats of the second generation under treatment with thymus extract. The grandparents and parents, therefore, had received injections of thymus extract. The biologic data concerning rats of the third generation are summarized in table 4.

Interval Between Gestations: Of the 5 pairs of animals bearing in the second generation, the first pair treated (rats 42 and 43) had 2

10. One additional pair (rats 36 and 37), observed for six months, had no offspring.

rate with gradual return to normal. The fall in the output of the left ventricle is accompanied by a systemic vasoconstriction, so that a fall of 10 mm. of mercury in the systemic pressure does not occur till the cardiac output is reduced by from 30 to 66 per cent,¹¹² and the cross-sectional area of the pulmonary artery must be reduced by from 61 to 86 per cent in order to produce this. Death does not follow until the cross-sectional area is reduced by from 84 to 96 per cent.

Again, in various species embolism of the pulmonary arterioles, due to the presence of multiple starch granules,⁸⁷ in amount just insufficient to cause immediate death (the animals all died in from one and one-quarter to eight hours) caused only transient changes in the right ventricular pressure; the output of the left heart was not constantly decreased and sometimes was actually increased. All these experiments show that great widening of the pulmonary vascular bed may occur by the dilatation of the vessels and the opening up of new ones, thus making possible a greatly increased flow of blood through the lungs without marked alteration in the blood pressure.

Respiration also plays an important part. In inspiration the negative intrathoracic pressure draws more blood into the right auricle. This causes an increased right ventricular output, which in the absence of compensatory factors would cause the pressure in the pulmonary artery to rise. But the reduced intrathoracic pressure causes a dilatation of the thin-walled left auricle and pulmonary veins, thus reducing the resistance to the flow of blood through the lungs. Some state that in inspiration the alveolar capillaries are lengthened and narrowed, thus increasing greatly the resistance in the pulmonary circulation. Cloetta concluded that in inspiration two opposing forces act on the alveolar capillaries: 1. A radial traction inward of the expanding alveoli which tends to dilate the vessels lying between them. When the alveoli are fully expanded, this is reversed and the capillaries are compressed. 2. A linear traction which lengthens and narrows the vessels. The net result is dilatation except at the end of inspiration, when the caliber is reduced. Daly⁷¹ excluded the effects of the heart by artificially perfusing the isolated lungs at a constant rate under negative pressure respiration. He found that inspiration caused a fall in the pressure in the pulmonary artery. Dunn⁸⁵ in intact goats also found that the minimum right ventricular pressure, systolic and diastolic, occurred at the height of inspiration. Thus the increased right ventricular output during inspiration is more than compensated for by the increased capacity of the pulmonary vascular bed, so that the pulmonary pressure falls. Great importance has been attached to the respiratory movements as an aid to the pulmonary circulation, and it is said that if free movements are impeded by pleural adhesions, the work of the right ventricle is so increased that it must become hypertrophic.⁶⁴

TABLE 4.—Rate of Development of Treated Albino Rats in the Third Generation (F₃)

Parents (No.)*	Period Between Gesta- tions, Days	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Teeth of Eruption	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Preg- nancy (Days from Birth)	Casting of First Litter (Days from Birth)	Comment
42 and 43 M T	37	6	6.1	6	1-2	1-2	4-6	5	12	31	9/25/33	78	90	
58 and 59 P P T	44	10	5.1	7	1	1-2	4-6	6	9	28	2/20/34	56	78	Crushed
	40	8	5.0	5	1-2	2	4	4	5	26	
		8	5.8	7	1	1	5	5	5	27	All females
62 and 63 P P T	42	11	5.4	11	1	1	5-6	6	13	30	1/19/34	78	87	
	45	10	5.1	8	2	2	3-5	5	21	32	1/19/34	72	94	
	25	7	5.0	6	1	1	4-6	6	8	23	2/20/34	48	70	Poorly nourished
	45	8	4.5	8	1	1	3-4	5	5	25	3/12/34	55	76	
		9	6.4	9	1	1	3-5	6	6	25-26	4/21/34	
68 and 69 M T	41	9	6.1	4	2	1-2	3-5	6	12	29	11/ 7/33	61	82	
	58	8	5.3	8	1-2	1	3-5	5	12	23	1/19/34	69	90	
	30	6	4.9	0	Neglected and unfed
		6	5.4	5	1-2	1-2	3-4	4	5	All males
80 and 91 M T	..	3	4.5	0	Unfed

* The letters M T indicate treated after maturity; P P T, treated before puberty.

the absence of heart failure, and Weiss,³²⁰ using Stewart's formula,²⁸⁹ calculated that the average volume of blood in the lungs was 24 per cent of the total volume of blood (normal, 11 to 21 per cent) and the vital capacity was decreased. This suggests that the resistance to the flow of blood through the lungs is increased.

The facts thus far mentioned show that the pulmonary circulation is largely regulated by the output of the right ventricle and the resistance in the left auricle and that the effects of these are greatly modified by the ready mechanical distensibility of the small pulmonary vessels, which prevents changes in the output and resistance from exerting their full effect on the pulmonary blood pressure. To what extent independent contraction of the pulmonary vessels in response to nervous or chemical stimuli influences the pulmonary circulation is still disputed. Many nerves accompany the pulmonary artery, though it cannot be assumed that these contain vasomotor fibers. But recent experiments seem definitely to have established the presence of vasomotor fibers to the pulmonary vessels of dogs. Daly,⁷³ in the isolated perfused lung of the dog with nervous connections intact, found that stimulation of the stellate ganglion caused pulmonary vasoconstriction, while stimulation of the cervical vagi caused sometimes vasoconstriction and sometimes feeble vasodilatation, but that these effects were obtained in only about half the preparations. The effects were sometimes obtained without simultaneous changes in the bronchi, showing that they were due to independent vasoconstriction and not to compression of the radicles of the pulmonary vein by contracting bronchial muscle. Hochrein and Keller¹³³ found that stimulation of the peripheral end of the vagus produced no change, while stimulation of the central end caused a reflex action through the sympathetic system which resulted in dilatation of the pulmonary arteries and an increase in the blood content of the lungs, but an unchanged or diminished outflow from the lungs, as a result either of a constriction of the pulmonary veins or of greater dilatation of the capillaries than of the arteries. The results are thus conflicting, but it seems probable that both constrictor and dilator fibers to the pulmonary vessels of the dog run in both the vagus and the sympathetic nerves.

ACTION OF DRUGS

Drugs produce varied effects according to dosage, species of animal, perfusion pressure, temperature and probably other factors,⁷² such as the integrity of the pulmonary nerves. If the bronchial vessels are not perfused as well as the pulmonary vessels, the nerves quickly die, and this may influence the results.

Epinephrine.—Franklin,¹⁰⁵ in his experiments on dogs for which he used rings cut from the pulmonary vessels and suspended in Ringer's solution, found that epinephrine usually caused contraction but some-

litters and since October 1933 has produced no more. The period between these gestations was thirty-seven days. In 1 prepubertal test pair (rats 58 and 59), there were 3 gestations, the intervals being forty-four and forty days, respectively. A second prepubertal test pair (rats 62 and 63) had 5 litters, the interval between gestations ranging from twenty-five to forty-five days, with the latter span the most unusual. A mature test pair (rats 68 and 69) had 4 litters, the interval between gestations ranging from thirty to fifty-eight days, with an average of forty-four days. Another mature test pair (rats 90 and 91) cast 1 litter. The average period between births for the generation as a whole was forty and a half days.

Size of Litters: The largest litter consisted of 11 animals. The average number of rats to the litter was 6.5 for the first pair, 8.7 for the second, 9.4 for the third, 7.5 for the fourth and 3 for the fifth, a total of 115 rats in 15 litters or an average of 7.6 rats per litter.

Weight at Birth: The average birth weight per litter was 5.3 Gm. for the prepubertal group (8 litters of 71 animals) and 5.1 for the mature group (7 litters of 44 animals). This gave a combined average birth weight per litter of 5.2 Gm. for the test pairs.

Survival of Offspring: Of the 115 offspring in the third generation, 84, or approximately 73 per cent, survived.

Opening of Ears: The ears usually opened on the first day; sometimes the process required two days for its completion.

Eruption of Incisors: The incisors usually erupted at about the same time that the ear lobes became detached, that is, from the first to the second day after birth, in most instances at 1 day of age.

Appearance of Fur: The hair obscured the genitalia as early as the third and as late as the sixth day; usually the fur appeared between the fourth and the fifth day.

Opening of Eyes: The eyes opened between the fourth and the sixth day; the earlier date was the usual one for the later litters.

Descent of Testes: In this group the time of the descent of both testes into the scrotum varied markedly from the fifth to the thirteenth day in most instances, but in 1 litter the descent occurred as late as the twenty-first day. Judging by the 2 groups of 5 litters cast, the date of the descent of the testes seems to become progressively more precocious with each succeeding litter. In the offspring of rats 62 and 63 the testes descended in the first litter at 13 days and in the fifth litter at 6 days. In the first litter of rats 68 and 69 the testes descended at 12 days, and in the fourth litter, at 5 days.

Opening of Vagina: In all the offspring of thymus-treated rats of the second generation the vagina opened earlier than normal. This phenomenon occurred between the twenty-third and the thirty-second

the changes in the veins tend to neutralize those in the arteries. They therefore expressed the belief that the pulmonary veins play no important part in regulating the blood content of the lungs. This does not follow from their findings. A drug injected into the circulation will stimulate all the nerve endings that it meets for which it is specific, but it is easy to imagine that normally the nerve fibers, dilator or constrictor, to the veins may be stimulated independently of those to the arteries.

Histamine.—The results of different observers and with different species are discordant. In the dog Nixon⁸⁰ found that histamine caused a rise in pulmonary arterial and left auricular pressure probably chiefly because of the increased cardiac output, though possibly the pulmonary arterioles also contracted. This was followed by a fall in the pulmonary arterial pressure due to the constriction of the hepatic veins, the distention of the liver and the diminished return of blood to the heart. Gaddum¹¹¹ found that histamine caused contraction of both arterioles and venules. Mautner¹⁰⁰ found that after the intravenous injection of histamine there were a simultaneous fall in the carotid arterial pressure, a rise in the pulmonary arterial pressure, a fall in the left auricular pressure and swelling of the lungs. These changes were attributed to constriction of the pulmonary veins which imprisons blood in the lungs and diminishes the inflow to the left heart. In the cat Dixon found a rise in the pulmonary arterial pressure due entirely to dilatation of the coronary vessels and a quicker return of blood to the right heart; while Gaddum found contraction of both arterioles and venules. In the rabbit Dixon found contraction of the arterioles.

Pituitary Extract.—Holtz¹³⁵ found that in the rabbit this caused a fall in the pulmonary arterial pressure owing to the diminished coronary flow and weakening of the heart; in cats, an increased pulmonary arterial pressure owing to increased coronary flow, and in dogs, a fall in pressure owing to a diminished coronary flow. In no case was an effect of the drug on the pulmonary vessels demonstrated.

Digitalis and Strophanthin.—Eppinger⁹⁸ found in guinea-pigs' lungs perfused with Locke's solution a constriction of the pulmonary vessels when 1.2 mg. per hundred cubic centimeters of digitoxin or strophanthin was added and dilatation when the concentration was only 0.1 mg. per hundred. He suggested that in man large doses of digitalis may cause spasm of the pulmonary vessels and failure of the right heart. To support this he cited 2 cases of auricular fibrillation with mild heart failure in which the failure increased under the influence of digitalis. In these cases the concentration of the alkaloids of digitalis in the blood must have been much less than 0.1 mg. per hundred cubic centimeters, which in the guinea-pig caused dilatation, not contraction, of the pulmonary vessels, but he suggested that there may have been an idiosyncrasy of

day and at a slightly earlier date in each succeeding litter. For instance, in the first litter of rats 68 and 69 the vagina opened on the thirtieth day, and in the fourth litter, between the twenty-fifth and the twenty-sixth day. The earliest opening of the vagina noted in any of the animals of the third generation was on the twenty-third day.

Growth Curve of Animals of the Third Generation: The growth of rats in the third generation was decidedly greater than that of the controls (fig. 2).

Summary of Data Relative to the Third Generation.—In summarizing the results of treatment as observed in animals of the third generation it is found that a striking acceleration of growth and develop-

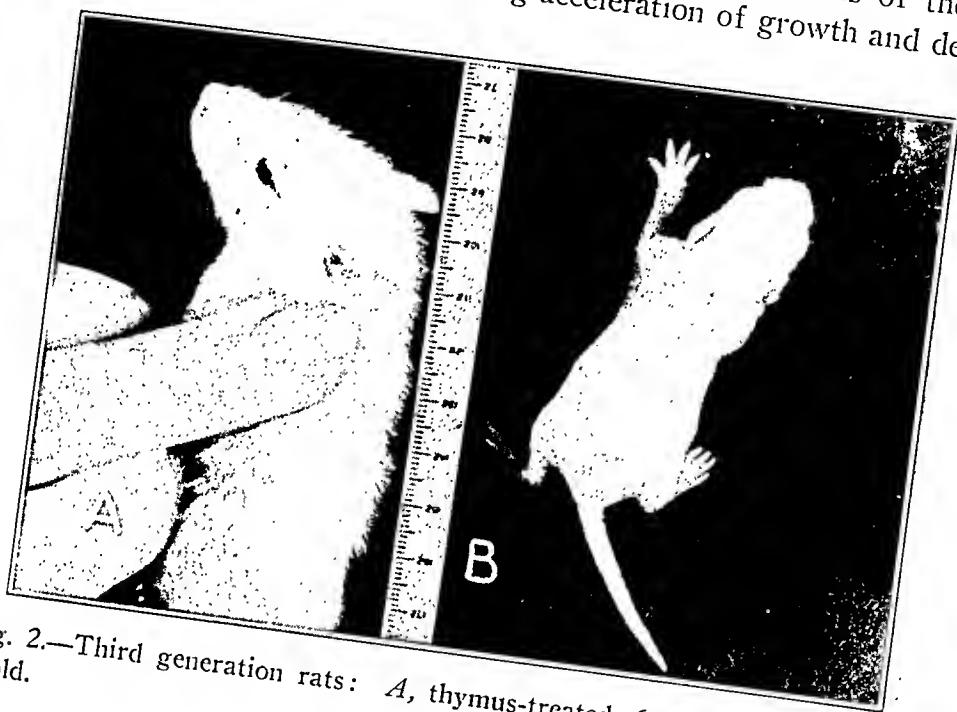


Fig. 2.—Third generation rats: A, thymus-treated, 6 days old; B, control, 7 days old.

ment occurred. The litters were larger (7.6 animals per litter); the birth weight, 5.2 Gm. per litter, and the rate of survival, 73 per cent, were high. The ears opened and the teeth erupted at the age of from 1 to 2 days; the animals were covered with hair at from 3 to 6 days; the eyes opened at from 4 to 6 days; the testes descended at from 5 to 13 days; the vagina opened at from 23 to 31 days. The animals grew much more rapidly than the control rats of the same group.

Data Relative to the Growth and Development in the Rats of the Fourth Generation (F_3).—The fourth generation consisted of 76 animals born in 12 litters to 5 pairs of rats treated with thymus extract. The great grandparents, grandparents and parents all received injections of thymus extract (Hanson). Biologic data concerning the rats of the fourth generation (F_3) are summarized in table 5.

wall which hinders gaseous exchange.) There would thus be no reason to expect a raised pulmonary blood pressure, and this would explain the frequent absence of hypertrophy of the right ventricle. Most observers, however, believe that the pulmonary capillaries are narrowed and reduced in number. This change, if advanced enough to use up all the "reserve capillaries," would throw a great strain on the right ventricle. Blumgart ³¹⁹ found that the circulation through the lungs was usually not slowed and was sometimes quickened. This shows that any obstruction in the pulmonary circulation was successfully overcome, especially as the systemic venous pressure was normal, but it does not show whether hypertrophy of the right ventricle was necessary to accomplish it.

FIBROSIS OF THE LUNGS

Fibrosis destroys many pulmonary capillaries, reduces the respiratory movements and perhaps embarrasses the heart by displacing it. Costa ⁶⁴ suggested that peribronchial fibrosis may obstruct the bronchial circulation, divert the bronchial blood into the pulmonary circulation and so raise the pulmonary blood pressure. Perhaps septic absorption from tuberculous or bronchiectatic cavities may weaken the heart. Many of the alveolar walls are thickened and lined by cubical epithelium. Any blood flowing through the walls of such alveoli must remain largely unoxygenated.

PLEURAL ADHESIONS

Costa ⁶⁴ and others have expressed the belief that obliteration by adhesions of both pleurae embarrasses the right ventricle by diminishing the respiratory movements and so diminishing the aid usually given by them to the flow of blood through the lungs. Dunn ⁸⁰ showed that pleural effusion increases the mean pulmonary diastolic pressure in goats, and Dubrow ⁸³ found that thoracoplasty in dogs leads to right axis deviation, as shown in the electrocardiogram.

HEART FAILURE

In the early stages of heart failure when there is dyspnea on exertion, there are no changes in the systemic arterial, capillary or venous pressure, in the cardiac output per minute, in the velocity of blood flow in the systemic vessels, in the cerebral circulation rate or in the blood chemistry.^e The only measurable early changes are a decrease in the vital capacity of the lungs and in the linear velocity of the blood flow through the lungs, the minute volume flow still being normal. These changes are due to dilatation of the small pulmonary vessels and the opening up of new capillaries. This causes rigidity and perhaps distention of the alveoli. The total volume of the lungs may be normal or even increased

(c) 127, 128, 318.

TABLE 5.—Rate of Development of Treated Albino Rats in the Fourth Generation (F₄)

Parents (No.)*	Period Between Gesta- tions, Days	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Eruption of Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Preg- nancy (Days from Birth)	Casting of First Litter (Days from Birth)	Comment
50 and 51 P P T	..	12/ 8/33	7	5.7	0	Died, unfed, injured
	29	1/ 6/34	10	5.3	9	1	1	2-6	6	11-2	24-25	1/31/34	25	44	..
	32	2/ 7/34	3	4.9	0	Unfed
	23	3/ 2/34	5	5.2	5	1	1	2-4	4	6	21	3/12/34	96
	33	4/ 4/34	8	5.0	5	1	1	2-5	5	5	All males
86 and 87 M T	..	3/16/34	4	5.0	4	1	1	4-6	6	6	27	4/ 3/34
76 and 77 M T	..	1/28/34	8	5.0	8	1	1	3-4	4	12	25	2/20/34	88	109	..
	47	3/16/34	3	6.0	2	1	1	2-4	4	6	All males
	23	4/ 8/34	4	6.0	4	1	1	2-4	4	5	All males
80 and 81	..	3/20/34	9	4.8	See comment		1	3-4	4	Died of starvation 5 days after birth
P P T	14	4/ 3/34	6	6.3	5	1	1	3-5	5	6	24
94 and 95 P P T	..	4/16/34	9	4.8	8	1	1	3-5	5	7	22

* The letters P P T indicate treated before puberty; M T, treated after maturity.

pressure was 90 mm. mercury systolic and 60 mm. diastolic. The liver and spleen were not enlarged. Moderate pressure over the muscles of the lower parts of the legs and the deltoid muscles caused the patient to cry out because of pain.

Course and Treatment.—The daily temperature, pulse rate, respiratory rate and blood pressure during the patient's stay of forty days in the hospital are shown in figure 1.

During the first three days in the ward the patient was stuporous. The heart sounds were weak, gallop rhythm persisted and the blood pressure declined. She was able to take only fluids by mouth. On the second day the cutaneous and

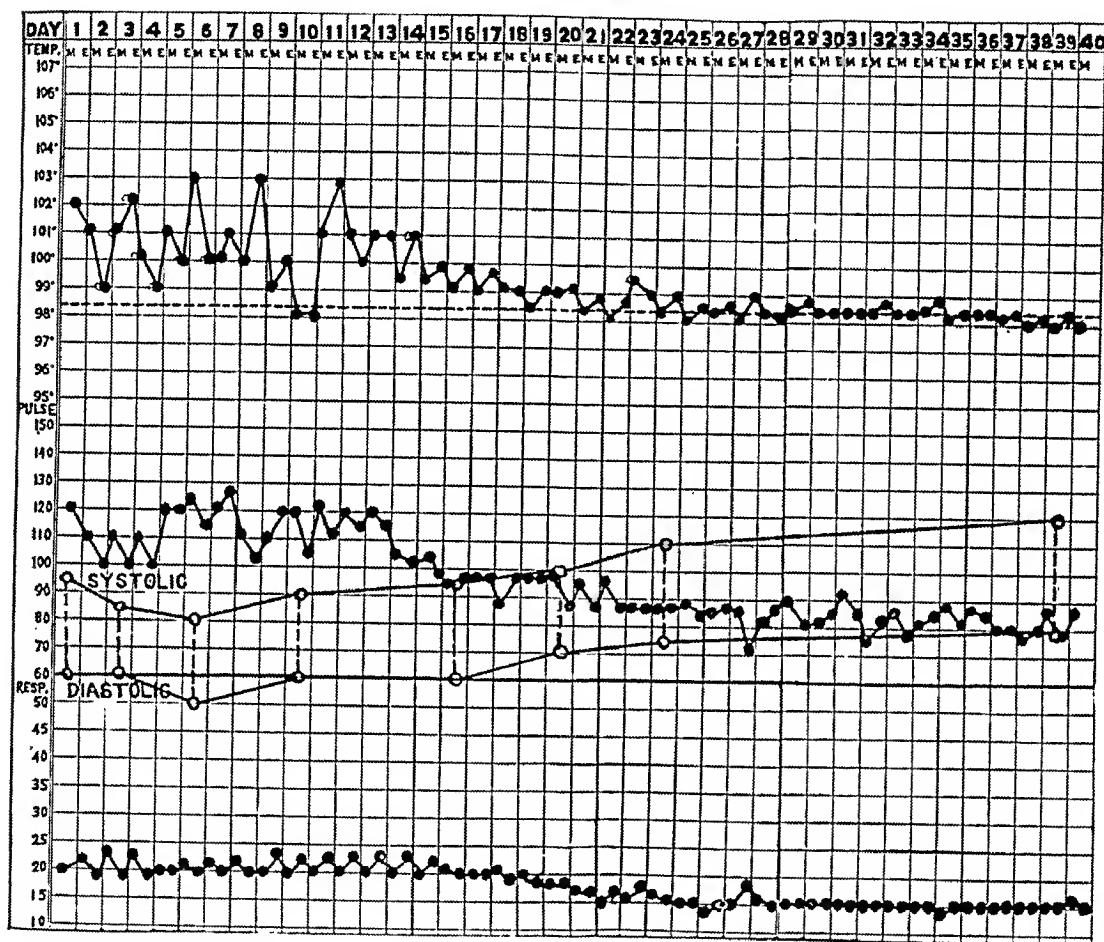


Fig. 1 (case 1).—Chart showing the daily temperature, pulse rate, respiratory rate and changes in blood pressure.

precipitin tests for trichinosis were markedly positive.² Because of the drop in blood pressure, the signs of a weakened myocardium and the patient's inability to take nourishment, she was given on the sixth day 300 cc. of a 10 per cent solution of dextrose intravenously and 15 units of insulin. The following day she was given 150 cc. of dextrose solution intravenously. After the second infusion the pulse rate dropped from 128 per minute to 104, the sounds at the apex were improved slightly in quality, and the rhythm was regular. The blood pressure began to rise. On the eleventh day 20 cc. of a 10 per cent solution of magnesium sulphate was administered intravenously. Two days later, or four weeks after the onset of her illness, the temperature and pulse began to decline progressively, as recorded

Interval Between Gestations: The interval between gestations in the third generation was as a rule relatively short and varied from twenty-three to forty-seven days. On two occasions it was twenty-eight days. The average interval for the group as a whole was twenty-three days.

Size of Litters: The litters of the fourth generation were not as large as those of the third. Only once were litters of 10 and 9 animals, respectively, encountered. The average number for the 12 litters was 6.3.

Weight at Birth: As a group the rats of the fourth generation were not larger at birth than those previously observed in the majority of instances. In one litter the average weight was 6.3 Gm. per animal. The average for the group of 78 animals was 5.3 Gm.

Survival of Offspring: Sixty per cent, or a total of 46 animals, survived.

Opening of Ears: The ears opened within twenty-four hours in every rat in the fourth generation.

Eruption of Incisors: The incisors erupted within twenty-four hours in every rat in the fourth generation.

Appearance of Fur: Fur appeared very early in the fourth generation of thymus-treated rats. It was quite marked on from the fourth to the sixth day in all the animals although it appeared from the second to the fourth day in the majority of cases. The rate of development of the hair was unbelievable in many instances; rats showing but a slight down in the morning often had a heavy growth of hair by evening or by the following morning. In the majority of these animals by the fourth or fifth day the fur was far more developed than in the majority of the control animals at the age of 16 days.

Opening of Eyes: The eyes opened on the fourth day in 4 litters, on the fifth day in 3 litters and on the sixth day in 2 litters.

Descent of Testes: The testes descended in some litters as early as the fifth day and in others as late as the twelfth day. In this connection the tables reveal an interesting and significant fact. The descent of the testes occurred much earlier in the litters subsequent to the first in all instances in which several litters of this generation were born to thymus-treated parents. Thus in the litters of the first pair (rats 50 and 51) it occurred on the eleventh and twelfth days in the second litter, on the sixth day in the fourth litter and on the fifth day in the fifth litter. In litters of the third pair (rats 76 and 77) it occurred on the twelfth day in the first, on the sixth day in the second and on the fifth day in the third. This is in keeping with the findings already recorded for testicular descent in the second and third generations of thymus-treated rats.

Opening of the Vagina: The vagina opened in the animals of the fourth generation at from the twenty-first to the twenty-seventh day.

the interval the T wave in lead II changed from inverted to upright and the voltage of the T wave in lead I and of the R wave in leads I and II increased.

Examinations of the urine and stool revealed no pertinent findings. Cultures of the blood were sterile. The nonprotein nitrogen of the blood was normal. The Kahn reaction of the blood was negative.

The erythrocytes on entry numbered 4,400,000 per cubic millimeter, and the hemoglobin content was 11.7 Gm. per hundred cubic centimeters of blood. The white blood cells numbered 10,800 per cubic millimeter, with 22 per cent polymorphonuclear eosinophils. For the first two weeks after admission the white cell count was persistently elevated, varying between 9,600 and 15,000 per cubic millimeter. The eosinophils reached a maximum of 50 per cent on the third day. Thereafter the number slowly declined until the twenty-third day when 2 per cent were present.

Subsequent Course.—The patient was seen seven months after leaving the hospital. She complained of weakness, pain in the muscles of the extremities, dyspnea and palpitation on exertion and slight edema of the ankles. Examination of the heart revealed the first apical sound slightly rough and the second sound snapping. The rate was regular. No murmurs were heard. The blood pressure was 106 mm. of mercury systolic and 70 mm. diastolic. An electrocardiogram was normal. The cutaneous test for trichinosis was positive.

The following case of trichinosis also showed electrocardiographic changes:

CASE 2.—History.—M. G., a 33 year old American housewife, seven days before entry ate some ham which had been cooked before purchase. The following day she was nauseated and suffered from generalized abdominal pain and diarrhea. On the third day of the illness the eyes became puffy and painful and photophobia developed. She had a severe headache and pain in the back of her neck. On the sixth day the patient complained of tenderness in the muscles of the legs, arms, shoulders and neck. For twenty-four hours before admission she experienced palpitation but no precordial pain or dyspnea. One other member of the family had mild symptoms indicative of trichinosis.

Physical Examination.—The patient was a well developed and obese woman in mild physical distress. The eyes were normal. There was tenderness on pressure over the region of the external rectus muscles but no demonstrable weakness. Tenderness was also elicited on pressure over the muscles of the neck and shoulders and of the lower part of the arms and legs. The heart and lungs appeared normal. The pulse was regular and soft, with a rate of 80 per minute. The blood pressure was 120 mm. of mercury systolic and 70 mm. diastolic.

Course and Treatment.—During the first four days in the hospital, the patient had temperature readings of from 99 to 100 F. in the evening. Thereafter there was no fever. The pulse rate for the first four days varied between 100 and 120 per minute, but fell to 80 per minute the day after fever ceased. The blood pressure remained the same throughout her stay in the hospital. The diarrhea subsided before entry, and constipation ensued. On the twelfth day of the disease the patient's reaction to an intradermal test with trichinella antigen was negative. Six days later the intradermal test was positive. On the nineteenth day of the infection, microscopic examination of a bit of tissue from the gastrocnemius muscle showed "foci of chronic inflammation; no parasites." The precipitin test of the blood serum was positive on the twenty-third day of the infection. During the third week of her illness the patient felt greatly improved, but in view of the electrocardio-

This phenomenon also occurred somewhat earlier in succeeding litters when several litters were born to the same pair. The earliest occurrence was at the age of 21 days, which is somewhat sooner than in the third generation, in which it occurred at 23 days.

Summary of Data Relative to the Fourth Generation.—From these observations it appears that the interval between the casting of litters was short (average twenty-eight days); the number of young in the litters was 6.3; the weight at birth was high, 5.3 Gm., and the rate of survival was 60 per cent. The ears opened and the incisors erupted within twenty-four hours; the animals were covered with hair by the fourth day;



Fig. 3.—Fourth generation rats: *A*, thymus-treated, 6 days old; *B*, control, 7 days old. The eyes of the thymus-treated rat are open.

the eyes opened at from the fourth to the sixth day; the testes descended at from the fifth to the twelfth day, and the vagina opened at from the twenty-first to the twenty-seventh day. The growth of these animals was markedly accelerated.

Data Relative to the Rate of Growth and Development of Rats of the Fifth Generation (F_4).—The fifth generation consisted of 21 rats born to 1 pair (rats 204 and 205), 9 in the first and 12 in the second litter. The interval between the casting of litters was forty-two days. All the rats of the first litter died of starvation at about 3 days of age, probably owing to lack of milk secondary to imperfect development of the mammary glands in a very young mother (43 days old). They lived

twenty-six cases were reviewed. As a result two more cases showing inversion of the T waves during the course of trichinosis may be added. In a third case, in which chronic rheumatic disease of the heart as well as trichinosis was present, the patient showed a temporary intraventricular block. Low amplitude of the QRS complex during the acute stage of the infection was present in a fourth case.

COMMENT

For several years the question has been raised whether the cardiac lesion of trichinosis is due to a direct invasion of the muscle by larvae or to blood-borne toxins. Zenker⁴ in 1860 first observed the larvae in the heart muscle of a patient in whom the disease had been fatal. Five years later Cohnheim⁵ described the cardiac lesion in another patient as that of parenchymatous degeneration. Frothingham⁶ in his description of the postmortem appearance of the myocardium stated that there are active cellular infiltration and necrosis of cardiac muscle. In one section he saw under the microscope part of a *Trichina* larva lying outside the vessels and muscle fibers.⁷ Prym⁸ found the larvae of *T. spiralis* in the myocardium of two patients who had died. Horlich and Bicknell⁹ reported the case of a patient dying of acute myocarditis in the fifth week of the disease. Larvae were observed microscopically in the cardiac muscle. It is significant that Prym⁸ found living larvae in the pericardiac fluid and that Gruber¹⁰ described a fatal case of trichinosis complicated by recent inflammatory lesions in the pericardium.

Other observers have reported similar observations in experiments on animals. Graham,¹¹ working with white rats infected with *T. spiralis*, observed inflammatory foci in the myocardium and larvae between the muscle fibers. The largest number of larvae were noted about the ninth

4. Zenker, F. A.: Ueber die Trichinen-Krankheit des Menschen, Virchows Arch. f. path. Anat. **18**:561, 1860.

5. Cohnheim, J.: Tödliche Trichinose mit parenchymatöser Degeneration von Leber, Herz und Nieren, Virchows Arch. f. path. Anat. **33**:447, 1865.

6. Frothingham, C.: A Contribution to the Knowledge of the Lesions Caused by *Trichina Spiralis* in Man, J. M. Research **15**:483, 1906.

7. Dr. F. B. Mallory permitted me to examine the original section and to see the larva to which Frothingham referred.

8. Prym, P.: Ueber Trichinose beim Menschen, Centralbl. f. allg. Path. u. path. Anat. **34**:89, 1923.

9. Horlich, S. S., and Bicknell, R. E.: Trichinosis with Widespread Infestation of Many Tissues, New England J. Med. **201**:816, 1929.

10. Gruber, G. B.: Ueber die Beteiligung des Herzens und der Gefäße an der menschlichen Trichinose, Zentralbl. f. Herz- u. Gefäßskr. **17**:319, 347, 359 and 381, 1925.

11. Graham, J. Y.: Beiträge zur Naturgeschichte der *Trichina Spiralis*, Arch. f. mikr. Anat. **50**:219, 1897.

long enough, however, to show striking precocity, namely opening of the eyes on the third day (table 6).

Our data on the rate of growth and development in the fifth generation are based on observations in 12 rats of the second litter. The weight at birth was 5.8 Gm. On the first inspection of the animals after birth, the ears were open and the incisors had erupted. The animals became covered with hair between the second and third day, the coat of fur being perfect within 72 hours. In the animals of the surviving group the eyes opened at between $2\frac{1}{2}$ and 3 days of age so that at 72 hours the eyes of all the animals were opened. The testes descended on the fourth day, and the vagina opened on the eighteenth day.

Weaning of Rats of the Fifth Generation on the Third Day: As the 12 animals in this litter had the eyes open on the third day, were

TABLE 6.—Rate of Development of the Fifth Generation (F_4)

Parents (No.)	Litter	Date of Birth	Number	Weight at Birth, Gm.	Number Surviving	Opening of Ears†	Eruption of Teeth	Appearance of Hair, Days	Opening of Eyes, Days	Descent of Testes, Days	Opening of Vagina, Days	Comment
204 and 205*	1	2/19/34	9	5.5	See remarks	Birth	Birth	2-3	2.5-3	4	18	All young dead on third day, unfed and neglected
	2	4/ 2/34	12	5.8	12	Birth	Birth	2-3	2.5-3	4	18	One pair weaned 4/5/34 and placed in separate cage for mating

* Treated before puberty.

† At first injection, or within twenty-four hours.

covered with fur and were extremely active and intelligent, it was thought worth while to attempt the weaning of 1 pair. Consequently 2 rats were removed from the mother and placed in a cage provided with a Petri dish for food and with small appropriate containers for milk and water. These rats wandered about the cage, walked through the Petri dish and stepped into the containers for milk and water. They began to lick the food, water and milk off their feet and bodies. Within a short time they ate and drank normally. There was no delay in their gain in weight. In fact, they continued to increase steadily in size and weight and gradually outdistanced all their litter mates. For four weeks they each weighed 2 Gm. more than any of their litter mates, and at 25 days of age they weighed 90 Gm., practically 150 per cent more than the control animals of the same age.

Summary of Data Relative to the Fifth Generation.—In summarizing the results of treatment in animals of the fifth generation it is evident

plicating myocarditis shows that death usually occurred between the fourth and the eighth week of infection.¹⁵

Gruber¹⁰ stated that the vascular system may be affected by trichinosis as follows: 1. Edema, especially of the face and eyes, may occur. 2. Congestion and hemorrhage are frequently seen in the conjunctivae and sclerae. Bloody diarrhea may result from a pronounced inflammatory hyperemia, limited chiefly to the ileum, as demonstrated by Zenker. 3. Hypotension has occurred, in which a decreased vascular tonus may persist well into convalescence. Gruber contended that this is a result of a toxic effect on the vasomotor centers and that the systolic pressure cannot be elevated by epinephrine or strychnine. However, Cheney¹⁶ succeeded in raising the blood pressure markedly with epinephrine in a severe case of trichinosis with hypotension. 4. Thrombosis and infarction may result, as shown by Rupperecht, who found peripheral venous thromboses in twelve cases of trichinosis. Gruber presented the findings in a fatal case of trichinosis in which severe myocarditis with a fresh thrombus in the ventricle occurred.

Herrick¹⁷ recorded a case of severe trichinosis complicated by a femoral phlebitis. Kilduffe, Barbash and Merendino¹⁸ observed a case of trichinosis complicated by femoral thrombosis which occurred about ten days after the onset of the disease. Amputation of the extremity was necessary, and the patient died. Postmortem examination showed that the left femoral and left external iliac vessels were thrombosed up to the point of bifurcation from the common iliac vessel. No trichinae were found in the clot. Graham¹¹ found the embryos in sections from a rat's artery.

Gruber and Gamper¹⁹ examined the brain of a patient who died of trichinosis. They found emboli with young larvae in them. The trichinosis was associated with acute myocarditis and thrombi on the endocardium. Another case, reported by Bloch and Hassin,²⁰ was that of a

15. Christeller: Fälle von Trichinose, *Deutsche med. Wchnschr.* **44**:869, 1918. Proskauer, cited by Strauss: Ueber Trichinose, *Berl. klin. Wchnsthr.* **58**:121, 1921. Weller, C. V., and Shaw, M.: Myocardial Failure Due to Trichinosis, *Tr. A. Am. Physicians* **47**:41, 1932. Prym,⁸ Zoller,¹² Simmons,¹³

16. Cheney, G.: Sporadic Trichinosis with Extreme Hypotension, *J. A. M. A.* **86**:1004 (April 3) 1926.

17. Herrick, W. W.: Review of Recent Studies in Trichinosis, *J. A. M. A.* **65**:1870 (Nov. 27) 1915.

18. Kilduffe, R. A.; Barbash, S., and Merendino, A. G.: A New Jersey Outbreak of Trichinosis with Report of a Case Complicated by Femoral Thrombosis, *Am. J. M. Sc.* **186**:794, 1933.

19. Gruber, G. B., and Gamper, E.: Ueber Gehirnveränderungen bei menschlicher Trichinose, *Verhandl. d. deutsch. path. Gesellsch.* **22**:219, 1927.

20. Bloch, L., and Hassin, G. B.: Trichinosis Complicated by Encephalitis, *M. Rec.* **91**:537, 1917.

that the weight at birth was very high (5.6 Gm.).¹¹ The ears were opened and the teeth erupted on the first inspection within twenty-four hours of birth, and the animals were covered with hair by the third day. The eyes opened at between $2\frac{1}{2}$ and 3 days of age; the testes descended by the fourth day, and the vagina was opened by the eighteenth day. Psychic as well as physical precocity was so striking in these rats that two of them were weaned successfully before 3 days of age, and their growth curve surpassed that of their litter mates left with the mother.

Effect of Intraperitoneal Injections of Thymus Extract on Weight.—A study of the weight curves indicates a deficiency in growth in our

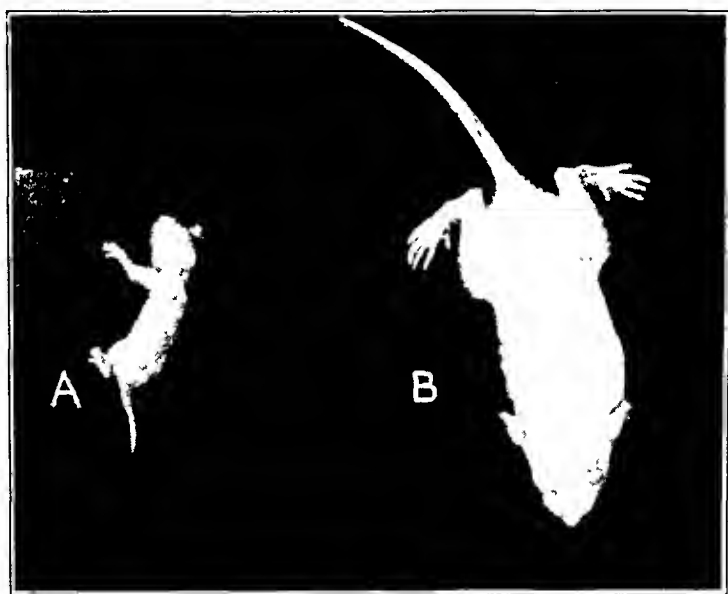


Fig. 4.—Fifth generation rats: *A*, control; *B*, thymus-treated, of same age as control.

control rats after the twentieth day as compared with the figures given by the Wistar Institute and a striking and increasing acceleration in the weight of our thymus-treated animals of the third, fourth and fifth generations and also in the later litters of the second generation. At all times from the fourth to the fortieth day our fifth generation rats weighed more than twice as much as our control rats and up to thirty days of age consistently outweighed the rats of the Wistar Institute. Between the third and the twentieth day our fifth generation rats exceeded the Wistar rats in weight by about 100 per cent. After the sixtieth day these curves tend to come together. These observations will be presented in a later publication.

11. This is the average weight for the group as a whole.

reported in detail by Beck and Cushing.⁵ In each of these patients the output of the heart was diminished as compared with normal values. In two of the cases, determinations were made also after the relief of the obstruction by operation. The output in one patient rose only slightly (from 1.79 to 2.05 liters); the output in the other patient rose significantly (from 2.11 to 2.96 liters). In each of these patients operation was followed by a reduction in the previously elevated venous pressure and by relief of symptoms.

The present report deals with the study of the circulation in a patient with *concretio cordis* before and after successful surgical treatment.

REPORT OF A CASE

A 17 year old Negro boy entered the Vanderbilt University Hospital on Oct. 5, 1933, complaining of swelling of the abdomen.

The illness had begun ten weeks before entry with fatigue, feverishness and lethargy which led the patient to take to his bed. On the same day he observed a vague discomfort in the epigastrium which shortly became a sharp and knifelike pain. This pain was increased by inspiration and accompanied by a feeling of breathlessness. It lasted four days and subsided gradually.

He then was permitted to get up, and he felt fairly well except for weakness. He failed to gain weight despite the fact that his appetite and digestion were good. Two weeks later (five weeks before entry) he observed a tight feeling around the abdomen; this persisted and increased. Several days later he fainted rather suddenly. He was again bedfast, and within a day or two it was observed that his abdomen was swelling and was tender to pressure. Both the swelling and the discomfort increased, and eight days before admission to the hospital $\frac{1}{2}$ gallon (1.89 liters) of clear fluid was removed from his abdomen.

In the five weeks preceding admission he had several attacks of nosebleed and a little cough, productive on two occasions of a small amount of blood.

His past history revealed excellent general health and strength. He had had measles, whooping cough, chicken pox and a respiratory infection called influenza. At no time had there been symptoms referable to the cardiorespiratory system. The family history was not helpful. There was no close association with known tuberculosis.

Physical examination revealed a tall, emaciated Negro boy. He appeared moderately uncomfortable. The temperature was 99 F., the pulse rate 110 and the respiratory rate 26. The skin gave evidence of recent loss of weight.

The retinal veins were distended, even when the patient sat up. The veins of the neck were both distended and firm. The thorax was symmetrical, but expansion was diminished. At the base of each lung the percussion note was flat; vocal fremitus was absent, and the breath sounds were diminished. These changes were more extensive at the base of the right lung.

The apex impulse of the heart was neither seen nor felt. The left border of dulness was 7 cm. from the midsternal line. The heart sounds were distant, regular and rapid. No murmurs or accentuations were heard. The radial pulse was small, quick and paradoxical. The blood pressure was approximately 106 systolic and 88 diastolic during expiration and 100 systolic and 90 diastolic during inspiration.

5. Beck, C. S., and Cushing, E. H.: *Circulatory Stasis of Intrapericardial Origin*, J. A. M. A. **102**:1543 (May 12) 1934.

difference in the degree of obstruction. Figure 2 illustrates the changes in venous pressure which took place during the period of observation and treatment. The period before operation was marked by a continuous rise in the venous pressure. Operation was followed by an immediate but transient drop in the venous pressure. The secondary rise in venous pressure was associated with the occurrence of hydrothorax and probably with a considerable reaction in the pericardium itself, with a consequent increase in the degree of obstruction. It appears that as this reaction subsided the obstruction was reduced, the venous pressure fell and the symptoms improved. When the patient was last seen, eight months after operation, the venous pressure as measured on the arm was found to be 125 mm. of water, a figure only slightly above normal.

The Output of the Heart and Related Functions Before and After Operation for Concretio Cordis

Date	Heart Rate	Oxygen Consumption per Minute, Cc.	Arteriovenous Oxygen Difference, Cc. per Liter	Output of the Heart		Venous Pressure (Arm), Mm. of Saline Solution
				Per Minute, Liters	Per Beat, Cc.	
11/24/33	...	207	96	2.16	..	376
11/27/33	116	217	104	2.09	18	...
11/29/33	Partial resection of pericardium					
1/27/34	118	235	92	2.54	22	239
2/ 3/34	118	233	74	3.16	27	...
2/ 6/34	114	238	80	2.86	25	...
2/21/34	108	271	72	3.79	35	200
3/ 5/34	208
4/ 4/34	186
7/ 9/34	125

STUDIES OF THE OUTPUT OF THE HEART

Measurements were made of the output of the heart by the acetylene method of Grollman, with the three sample technic introduced by Grollman, Friedman, Clark and Harrison.⁸ The results are summarized in the table.⁹

Before the operation which released the heart from the fibrous tissue which encircled it the output of the heart was about 2.1 liters per minute; the output per beat (the stroke volume) was only 20 cc.; the arteriovenous difference (the oxygen utilization) was 100 cc. per liter. The patient thus had a small output per minute, a very small output per beat and a high arteriovenous difference. The figures are comparable to those observed in similar cases by Burwell and Strayhorn and by Maltby.

After the operation four determinations of the cardiac output were made. The total output varied between 2.5 and 3.8 liters, and the

8. Grollman, Arthur; Friedman, Ben; Clark, Gurney, and Harrison, T. R.: A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, *J. Clin. Investigation* 12:751 (Sept.) 1933.

9. Dr. Ben Friedman and Dr. Harry Resnik Jr. made these determinations.

RESULTS IN A SECOND SERIES OF RATS UNDER CONTINUOUS TREATMENT
WITH DAILY INTRAPERITONEAL INJECTIONS OF THE SAME PREP-
ARATION OF THYMUS EXTRACT (HANSON)—SERIES 1 B

The results of injection of thymus extract in our first series of rats seemed so incredible that we believed confirmatory experiments were necessary. A conference was held with Dr. H. H. Donaldson as soon as the precocity of our third generation test rats was noted. At this conference it was decided to continue the treatment of the original group until 10 litters could be studied and to repeat the experiments starting de novo.

Accordingly, a pair of rats received injections of thymus extract beginning on Dec. 11, 1933. The geneological chart together with the data pertaining to the third generation is shown in table 7. Interest

TABLE 7.—*Second Series of Thymus-Treated Rats**

Geneology							
Rats 74 and 75 (born 8/30/33) — M. T. — L ₀ F ₀							
L ₁ born 11/11/33 — L ₂ — F ₁							
Rats 212 and 213 — M. T. — F ₂							
L ₁ — L ₂ — L ₃ — F ₂							
Litter	Date of Birth	Weight at Birth, Gm.	Opening of Ears	Appearance of Hair	Opening of Eyes	Number in Litter	Comment
L ₁ F ₂	2/22/34	5.3	3	All dead on second day
L ₂ F ₂	3/16/34	4.8	1-2	3-5	6	10	All died of inanition by seventeenth day
L ₃ F ₂	4/10/34	4.9	1	3-5	5	10	All died of inanition by twelfth day

* In this table "M T" indicates that the rats were treated after they had reached maturity.

centers, of course, on the third generation of thymus-treated rats, the generation which revealed such striking evidence in our original studies.

The period between gestations was short, varying from twenty-two to twenty-five days. Three litters were born between Feb. 22 and April 10, 1934. The average number of rats per litter was 7.6, and the average weight at birth was 5 Gm. The ears opened within two days. The animals were covered with fur in from three to five days, and the eyes opened on from the fifth to the sixth day. While not so extensive as before, these experiments yielded confirmation of our earlier results as to precocity, growth and development in the young of the third generation.

EXPERIMENT WITH A NEW PREPARATION OF THYMUS EXTRACT
(HANSON)—SERIES 1 C

All the results so far described have been obtained with the original preparation of thymus extract sent to us by Hanson. As stated, this extract was prepared in 1930 and hence had stood for about two and

seen in patients with severe chronic failure but are not seen in acute circulatory collapse except when the latter is due to cardiac tamponade, in which case there is obstruction, or to coronary occlusion, in which case there is heart failure. When occurring in chronic disease the combination of the evidence of markedly diminished cardiac output with the evidence of severe venous congestion usually indicates pericardial obstruction to the entry of blood into the heart. When, in addition, there is little or no enlargement of the heart, pulmonary congestion is slight as compared to peripheral congestion; signs of valvular disease are absent; the heart is fixed and pulsates little, and a pulsus paradoxus is present; the picture is distinctive enough for confident diagnosis.

Moreover, in *concretio cordis* venous congestion and venous pressure often attain degrees which are rare in so-called congestive failure. Thus in the patient under discussion the venous pressure was as high as 390 mm. of salt solution or about 30 mm. of mercury. Furthermore, like others of our patients with *concretio cordis*, he had a history of recurrent nosebleed during the period of his present illness, and the retinal veins were visibly distended even when he was sitting erect with the retina approximately 250 mm. above the right auricle.

But it is the combination of this high degree of congestion with the feeble pulse and diminished pulse pressure (evidences of diminished cardiac output) that points toward the diagnosis of pericarditis with obstruction.

This discussion has dealt with the alterations in circulatory dynamics associated with *concretio cordis*. In the main these alterations are similar to those brought about by fluid in the pericardium, which were so precisely described by Cohnheim.¹¹ In this instance also, especially when the fluid accumulates rapidly, the signs of congestion are observed in combination with the signs of diminished output. The conditions are to be differentiated mainly by examination of the heart, it not being forgotten that chronic pericarditis may begin with an obstructing effusion and terminate with an obstructing scar.

SUMMARY

A case is reported in which a high degree of obstructing pericarditis was present. This pericarditis was due to infection of the pericardium with *Staph. aureus*. Removal of a portion of the pericardium was followed by a fall in venous pressure, a rise in cardiac output and an increase in pulsation of the heart. Increased venous pressure and decreased cardiac output appear to be the chief mechanisms underlying the symptoms and signs of *concretio cordis*.

11. Cohnheim, Julius: *Lectures on General Pathology*, London, New Sydenham Society, 1889.

TABLE 8.—*Effect of Injection of Thymus Extract (New) on Albino Rats of the Second Generation (F₁)*

Parents (No.) 74 and 75	Litter	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Date of Pregnancy	Date of Casting of First Litter	Comment
	2	2/18/34	5	4.9	0	1/31/34	2/ 1/34	2/22/34	Extravasations about the face and belly
100 and 101	1	12/27/33	7	4.0	0
	2	2/18/34	7	5.1	3	3	9	11-13	13	27	3/12/34	Unfed; no milk
	3	3/23/34	5	4.6	0	Mated pair died 3/17/34; toxle
102 and 103	1	1/25/34	4	5.1	0	Neglected
	2	3/ 2/34	7	4.3	0
	3	4/10/34	4	5.0	4	2	8	9-11	11	15	44	5/28/34	3 crushed at birth; 1 died next day No milk

and posterior part of the lower lobe is a spot only second in point of vulnerability to the apex itself."

Of greater significance, however, than cases of secondary involvement of the lower lobe in the course of a progressive lesion of the upper lobe are those cases in which the lesion of the lower lobe represents the initial manifestation of bronchogenous tuberculosis. It is of interest to note that Kidd¹³ as early as 1886 emphasized the importance of the apex of the lower lobe as a site of predilection for early tuberculous changes, in contrast to the base of the lung. This author called attention to the fact that while lesions in the latter location are extremely rare, the former region is "very prone to disease and may be attacked before the apex of the upper lobe." More recently the significance of the apex of the lower lobe as a site of early changes has been stressed by Graeff and Kuepferle,⁷ Pohl¹⁴ and Assmann.¹⁵ Sweany, Cook and Kegerreis¹⁶ called attention to the situation of early cavities in that area. Other observations on tuberculosis of the lower lobe and basal tuberculosis were contributed by Rosenblatt,¹⁷ Middleton,¹⁸ Dunham and Norton,¹⁹ Colton²⁰ and Jacob.²¹

This study is based chiefly on the material of the department of tuberculosis of the Metropolitan Hospital over a period of four years. The prime object of investigation were the cases which presented sufficiently definite evidence that the process actually began in the lower lobe. There were thirty-four cases of this group, which will be referred to here as cases of primary lesions of the lower lobe. (The term primary in this connection is not to be confused, of course, with the primary tuberculous infection.) In an appreciable number of additional cases the evidence in favor of the origin of the lesion in the lower lobe was equivocal because of the advanced phase of the disease. There was also a small group of cases showing either very slight apical

13. Kidd, P.: On Basic Tuberculous Phthisis. *Lancet* **2**:615 and 665, 1886.

14. Pohl, R.: Ueber die Formen der bronchogenen Phthise mit Beginn im Unterlappen, *Beitr. z. Klin. d. Tuberk.* **59**:229, 1928.

15. Assmann, H.: Frühinfiltrat, *Ergebn. d. ges. Tuberk.* **1**:115, 1930.

16. Sweany, H.; Cook, C. E., and Kegerreis, R.: A Study of the Position of Primary Cavities in Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **24**:558 (Nov.) 1931.

17. Rosenblatt, J.: Chronic Pulmonary Tuberculosis Primarily in the Lower Lobe, *J. A. M. A.* **76**:1647 (June 11) 1921.

18. Middleton, W. S.: Lower Lobe Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **7**:307 (July) 1923.

19. Dunham, K., and Norton, V. V.: Basal Tuberculosis, *J. A. M. A.* **89**:1573 (Nov. 5) 1927.

20. Colton, W. A.: Basal Lesions in Pulmonary Tuberculosis with Report of 7 Cases, *U. S. Vet. Bur. M. Bull.* **4**:503 (June) 1928.

21. Jacob, M.: Lower Lobe Pulmonary Tuberculosis, *M. J. & Rec.* **129**:32 (Jan. 2) 1929.

a half to four years before being used. The new preparation of thymus extract was received on Jan. 6, 1934. It was administered intraperitoneally in doses of 1 cc. daily as in the other studies recorded. The treatment has been continued for from four to six months.

The six rats used in this series were born of rats which had received injections of the old thymus extract and represent the second and third (F_1 and F_2) generations under treatment. The results of this experiment were entirely negative as to evidence of precocity in growth and development (table 8). From this it appears that the new preparation of thymus extract was lacking in potency; why, we cannot say. One difference between the old extract prepared by Hanson himself and the new preparation is that Hanson's original extract contained 15.8 mg. per hundred cubic centimeters of reduced and oxidized sulphur compounds calculated as glutathione and this was lacking in the new preparation. This difference may or may not be significant, but the glutathione^{11a} content of the extract will be observed in future studies.

EFFECTS OF INTERRUPTION OF TREATMENT OF RATS WITH THYMUS EXTRACT (HANSON)

An effort has been made to determine the effect of omitting the treatment through one or more generations. The results of the studies in the group in which treatment was interrupted are shown in table 9.¹²

Observations on a TC Group.—The first group consisted of the offspring of control patients descended from treated grandparents. In this group there were 7 pairs. The shortest period between pregnancies in this group was twenty-four days; the longest, one hundred and eighty-six days. The largest litter consisted of 11 rats and the smallest of 3. There were 14 litters (90 animals) born of 7 pairs; the average weight at birth was 5.1 Gm. Of the 90 animals, 47 (52 per cent) survived. The ears opened at from the second to the third day. The teeth erupted as early as the third but usually from the eighth to the tenth day. Hair appeared late, from the tenth to the fourteenth day in all the animals except in litters from 1 pair in which it appeared from the third to the fifth day. The eyes opened on from the thirteenth to the fourteenth day in all but the animals born of 1 pair, in which they opened at 5 days in the first litter and at 10 days in the second litter. The testes descended at from the twentieth to the fortieth day in all except the offspring of 1 pair, in which they descended at 12 days in the first litter and at 18 days in the second litter. The vagina opened at ages varying from 20 to 60 days.

11a. Experiments in which glutathione is being used instead of thymus extract are now in progress.

12. In table 9 and in the text T indicates a generation treated with thymus extract, and C represents a control generation, a period with omission of treatment.

It appears, therefore, that the question as to the relative occurrence of tuberculosis of the lower lobe in the sexes is probably of greater significance than that concerning the total incidence. A true index can be arrived at only by a separate consideration of the male and female material. The occurrence of primary involvement of the lower lobe can thus be regarded as extremely rare in men. In women, on the other hand, although these lesions are by no means common, they seem to represent a distinct entity. It may furthermore be of interest that in the cases in which the lower lobe was found to be secondarily involved the discrepancy between men and women, though still present, was much less apparent.

As to the racial distribution, there were twenty-four white patients as against ten Negroes in this group. This relation corresponds closely with the general distribution of the patients in the institution. Thus, in contrast to the findings of Dunham and Norton,¹⁹ no predominance of the colored race could be noted.

The distribution according to age reveals that about two-thirds of the patients of this group were between 17 and 30 years of age; there was only one patient in the fifth decade of life and two in the sixth, the latter being patients with silicosis. The youngest patient was 17, the oldest 59. The average age of 29 years found in this group does not represent any deviation from the age incidence observed in corresponding forms of pulmonary tuberculosis in general. The statements of some authors (Dunham and Norton¹⁹ and Jacob²¹) who expressed the belief that tuberculosis of the lower lobe is peculiar to juveniles, are not borne out by this series of cases.

An analysis as to the duration of the symptoms revealed that the majority of the cases represented early phases of the disease. In more than one half, or eighteen cases, the patients dated their illness back for a period between two to eight weeks; in four cases the symptoms were present for three months, in nine for a period ranging between four and nine months, and in only three cases could the symptoms be traced back over a period of more than nine months.

The mode of onset, although showing no characteristic features which would definitely distinguish it from the types seen in cases with more common locations of the lesion, was noteworthy because of the rather acute griplike or pneumonia-like syndrome presented by a number of patients in the initial phase of the disease. This, however, is not infrequently observed in the early exudative and caseous forms of tuberculosis in general and cannot be regarded as peculiar to any particular location.

The physical signs are pronounced and easily detectable in the patients who show extensive involvement of the lower lobe. In patients with involvement of a relatively small area, especially in those in whom

TABLE 9.—Rate of Development of the Albino Rats Under the Influence of Thymus Extract (Hanson) When Treatment is Interrupted Through One or More Generations*

Parents (No.)	Litter	Period Between Gestations, Days	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Preg- nancy First Litter (Days from Birth)	Comment
34 and 55 P P C T-C	1	27	12/14/34	6	4.5	0
60 and 61 P P C T-C	2	35	1/10/34	11	4.9	0
64 and 65 P P C T-C	1	38	1/18/34	5	5.5	0
	2	38	2/22/34	7	4.4	0
	3	33	11/15/33	8	4.6	4	2-3	7-9	14	14
	4	28	1/23/34	3	4.1	4	2-5	9	10-12	40
	5	34	2/22/34	6	4.3	0	13	60
	1	..	4/16/34	7	5.3	9	36-40
	4/ 9/34	5	4.6	7	2	8-10	12-14
98 and 99 P P C T-C	1	187	9/10/33	4	6.3	0	14	39	45
	2	..	3/16/34	3	5.8	4	2	..	14	35
92 and 93 M C T-C	1	..	4/ 2/34	6	5.5	3	2
202 and 203 P P C T-C	1	..	4/ 3/34	8	6.2	6	2-5	3	5	12
52 and 53 P P C T-C	1	..	12/ 8/33	5	6.0	0	10	18
	2	54	1/31/34	1	5.9	0	14	28
	3	23	2/23/34	2	7.0	0
	4	24	3/19/34	3	4.6	0
72 and 73 P P C T-C	1	29	1/23/34	6	5.2	0
	2	..	2/21/34	5	4.7	4
	..	33	12/ 8/33	8	6.0	0
	3	42	1/10/34	10	4.6	0
	4	25	2/11/34	1	6.9	0
114 and 115 P P T T-C-T	1	..	3/ 6/34	7	5.4	0
	2	..	4/29/34	10	5.5	7
214 and 215 M C C T-C	1	..	2/19/34	9	9	2	2
	2	37	3/28/34	2	0	2-5	10	12-16	37
	3	19	4/16/34	13	1.3	2-5	34
210 and 211 P P C T-C T-C	1	..	4/10/34	3	3	3	7-8	9-12	32
	2	23	3/16/34	1	0
206 and 207 P P C T T-C	1	..	4/ 8/34	8	5.1	2	5	10-12	20
	2

* The data in the table relate to the offspring of the pair signified in the first column to the left. The symbols refer directly to parents, grandparents, great grandparents, etc. The last symbol in each sequence, C or T, refers to parents, the next to the left to grandparents, the next to the left to great grandparents, etc. All animals whose parents are test animals, whose grandparents are control animals and whose great grandparents are test animals, P C T P indicates that the animals are test animals, P C indicates control animals for the group treated before puberty; M C, controls for the group treated after maturity.

Cavities located in the apex of the lower lobe are remarkable for the large size which they seem to attain within a comparatively short period. In this connection it may be of interest to cite an observation of Aschoff,²³ who found that the reinfection foci situated in more caudate portions of the lung are, as a rule, larger than those located nearer the summit. This was also observed by Assmann¹⁵ in roentgenologic studies of early infiltrations. It should not be overlooked, of course, that the routine roentgenogram taken in the dorsoventral position is bound to exaggerate the size to a certain extent because of the location of the apex of the lower lobe close to the posterior wall of the chest. In cavities projecting near the root on the right side their relation to the interlobar fissure between the upper and middle lobes should be noted. If the horizontal fissure line is seen extending across the annular shadow



Fig. 6 (female, aged 26).—The postero-anterior view (A) shows a cavity on the right side directly over the hilus and focal infiltration through the lower half of the right lung and in the midfield of the left lung. Note the crossing of the cavity by the line of the interlobar fissure. The lateral view (B) demonstrates the cavity posteriorly over the spinal column, the location corresponding with the apex of lower lobe. There is a small collection of air posteriorly and above the diaphragm, due to initial pneumothorax.

this is practically a conclusive sign that the cavity is situated posteriorly within the apex of the lower lobe (fig. 6).

That the apex and subapical area of the lower lobe represent a distinct site of predilection for tuberculous involvement is also demonstrated in patients with more or less acute and massive lesions of the lower lobe in whom the earliest as well as the largest cavitations are, as a rule, found at or near the apex. In such cases the cavity may

23. Aschoff, L.: Ueber den phthisischen Reinfekt der Lungen. *Klin. Wchnschr.* 8:1 (Jan. 1) 1929.

This analysis indicates that the precocity observed in the third generation of rats born of control parents but of treated grandparents was confined largely to the offspring of 1 pair (rats 44 and 45). The parents were left with the grandparents, the mother nursing from the grandmother until a few days prior to the birth of the first litter. This first litter (L_1) showed considerable precocity as evidenced by the appearance of hair at the age of from 3 to 5 days, the opening of the eyes at 5 days, the descent of the testes at 12 days and the opening of the vagina at 31 days. However, the second litter born six months later to these same parents showed a marked diminution in this precocity, hair appearing at from 4 to 5 days, the eyes opening at 10 days and the testes descending at 18 days.

Observations on T T C Groups.—In two series of animals the parents were not treated, but the grandparents and great grandparents (rats 52 and 53 and rats 72 and 73) had received treatment. The offspring represented the fourth generation under observation. The parents and their litter mates showed marked precocity. Precocity in the offspring of these animals was not pronounced. One pair (rats 72 and 73) had two litters, consisting of 6 and 5 animals, respectively. The average weight at birth was 4.9 Gm. Only 4 animals (second litter) survived. The ears opened at the age of $2\frac{1}{2}$ days; the teeth erupted at 8 days; hair appeared at from 10 to 12 days; the testes descended at 26 days, and the vagina opened at 39 days. Five successive litters born to rats 52 and 53 died within three days of birth owing to neglect on the part of the mother. This may possibly have been due to the lack of milk.

Observations on a T C-T Group.—The next group also comprised the offspring of 1 pair (rats 54 and 55) on which treatment was begun pre-pubertally. The shortest time between pregnancies was twenty-three days and the longest thirty-three days. The number of litters was 4 and the number of young 26. The average weight at birth was 5.7 Gm. The number surviving was 17, or 65 per cent. In this group the precocity was very striking. The ears opened on the first day, the teeth erupted on the first day, the hair appeared from the second to the fifth day and the eyes opened on the fifth day in every instance. The testes descended at from the seventh to the seventeenth day, and the vagina opened at from the twenty-fourth to the twenty-fifth day. From this it appears that fourth generation rats born of treated parents and great grandparents but of untreated grandparents show striking precocity.

In contrast to this group there were several series of rats in which no treatment had been given except to the grandparents or earlier forebears. The groups are designated as CTC, TCTC and TTTC. Only slight precocity, if any, was encountered in these animals. From analysis of table 9, giving data on 173 animals born in 31 litters to 13

more or less diffuse distribution of foci of the acinous or sublobular type through the remaining area of the lower lobe, often extending down to the extreme base (figs. 5 and 6). This represents a spread by aspiration through the bronchial ramifications of the lower lobe. Other common sites of secondary involvement are the peripheral portions of the upper lobes in the vicinity of the lobar margins, more often from the right to the left side than vice versa. Secondary involvement of the apex of the upper lobe is also not infrequently observed.

It is very probable that the unfavorable conditions of drainage of the apical branches of the bronchus of the lower lobe and the resulting stagnation of infectious material in the cavities play a rôle in promoting spread by aspiration. In cases with a bronchogenous spread in the

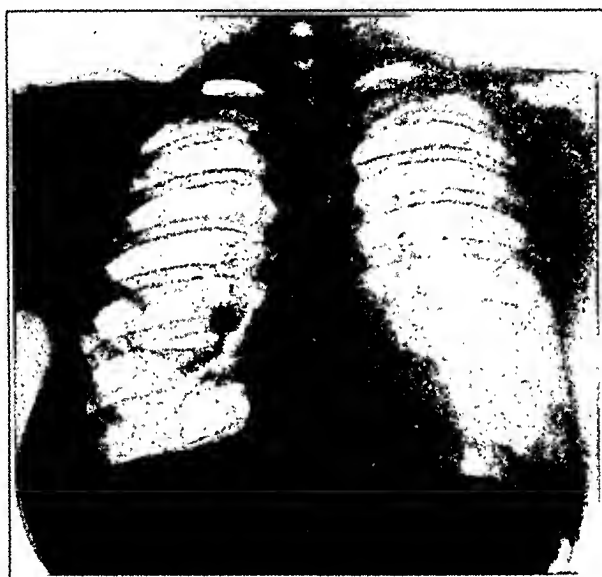


Fig. 8 (female, aged 26).—Roentgenogram showing an early tuberculous cavity in the midfield of the right lung close to the area of the root, with a collection of fluid resembling a nontuberculous abscess; there were no other pulmonary findings. Note the crossing of the cavity by the interlobar fissure, as in figure 6. Further study revealed that the cavity was located in the apex of the lower lobe.

cranial direction from the cavity the cough may be an important factor, a point particularly stressed by Tendeloo.⁸ It is evident that lesions of the lower lobe in the advanced stages with extensive progression may present an appearance which is hardly characteristic. In the absence of a preceding follow-up series a spread from above downward is easily assumed in such instances (fig. 9).

Occasionally tuberculous infiltration involving other pulmonary areas than the cranial portion of the lower lobe may also give rise to the roentgen appearance which resembles a hilus lesion. This is the case if the changes are situated in the medial portions of the upper lobes

pairs in the series in which treatment was interrupted for one or more generations, it is evident that precocity is lacking or is but slight in all animals born of untreated parents. The effects of treatment through three generations are largely nullified through omission of treatment of the fourth generation. When the effect of treatment is apparent in the offspring of untreated animals it appears, as a rule, only in the first litter, rapidly disappearing in succeeding litters. It seems likely, therefore, that when thymus treatment is discontinued in the parents the effect on the subsequent offspring is quickly apparent.

EXPERIMENTS ON ORAL ADMINISTRATION OF THYMUS EXTRACT

An effort was made to determine whether or not thymus extract is effective when administered by mouth. In order to determine its activity,

TABLE 10.—*Effect of Feeding Thymus Extract (New) on Albino Rats of the Second Generation (F₁)*

Parents (No.)	Litter	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Eruption of Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating
300 and 301	1	3/20/34	6	5.3	6	2	4	9-11	13	26	46	4/16/34
302 and 303	1	3/16/34	6	5.2	6	2	2	10-12	12	29	40	4/20/34
304 and 305	1	2/13/34	9	4.4	6	12	2	8-10	9-10	26	35	3/23/34
306 and 307	1	3/10/34	12	6.8	12	12	8	10	12	23	40	4/20/34

the extract was administered orally to 4 pairs of rats, all of which were born of animals having received old thymus extract by injection. In other words, these 4 pairs of animals represented second generation (F₁) rats under thymus treatment. These pairs, had treatment with the old extract been continued by injection, would in all probability have shown the marked precocity already recorded for our third generation (F₂) of thymus-treated rats. Four cubic centimeters of the new thymus extract per rat was administered daily mixed with the food over a period of four months. The food was not entirely consumed each day. Unfortunately only the new thymus extract was used in these experiments and since, as indicated, this was not potent when administered by injection, the results of this study must be considered inconclusive (table 10).

COMMENT

In this communication we have presented detailed evidence of the effect of thymus extract (Hanson) on the growth and development of rats born to succeeding generations of parents under treatment. It is obvious that there is an accruing acceleration of these effects in each

PROGNOSIS AND THERAPY

In answering the question whether or not there are any distinct differences with respect to the prognosis between tuberculosis of the lower lobe and the more common lesions of the upper lobe, certain limitations must not be lost sight of. In the first place, because of the comparatively small number of cases of primary involvement of the lower lobe the value of data gathered by a single observer is necessarily limited. Secondly, the measures of collapse therapy which most of the patients undergo are naturally bound to alter the spontaneous course of the disease. There are, nevertheless, several points which should be stressed here. The prognosis in pulmonary tuberculosis depends largely on the anatomic character of the lesion and the extent of the involvement. It is therefore important to recall, as has already been stated, that practically all the patients, of this group exhibited changes of the caseous-cavernous form, and that the cavitations seem to develop in the early phase of the disease and attain a rather large size. Furthermore, there is a distinct tendency toward further spread, with frequent involvement of the contralateral lung. In general, however, the course and ultimate fate in cases of lesions of the lower lobe are probably not different from those in cases in which the lesion originates in the upper lobe, provided that the nature and extent of the involvement are of a corresponding type, a point also noted by Pohl.¹⁴ True, in several cases of this series there could be observed massive caseous pneumonic lesions of the lower lobe, with rapid progression and a fatal event after a comparatively brief period of illness. The identical course, however, may take place if a lesion of a similar type involves the upper lobe.

Considering thus the character of the lesion, it is evident that early application of measures to bring about a collapse of the diseased portion of the lung is most essential. As to the procedure to be adopted, artificial pneumothorax seems to offer the best results. Because of the location in the lower lobe, phrenic neurectomy was employed as the initial measure in eight cases of this group; a satisfactory result with closure of the cavity was obtained in one instance only. Pneumothorax was instituted in nineteen of thirty-four cases of primary lesions of the lower lobe. In eleven cases a satisfactory result was obtained. In one case the result was doubtful, and in one case pneumothorax had to be discontinued because of circulatory embarrassment. In six cases the result was considered unsatisfactory because of failure to obtain closure of the cavities. It is interesting to note that in several instances in the group of failures, although no demonstrable adhesions were present, the cavities could not be collapsed. This behavior may have some connection with the location of the lesion, although no adequate explanation can be offered as yet.

generation. This is strikingly demonstrated in tables 11 and 12. The effect on weight has already been shown in the growth curves.

From our own investigations no claims can be made for the specificity of the thymus extract in connection with the acceleration in growth and development observed. Neither is it apparent whether the extract represents a secretory product, a physiologic hormone of the thymus or a pharmacodynamic agent derived from the thymus.

TABLE 11.—*Comparison of Data on Thymus-Treated Rats with Data on Control Animals*

	Control Animals	F ₁ *	F ₂	F ₃	F ₄
Number of pairs treated.....	4	4	5	5	1
Number of litters.....	21	17	15	12	2
Number of young.....	103	124	115	76	21
Average number per litter.....	4.9	7.3	7.6	6.3	10.5
Percentage of survival.....	37.8	58	73	60	57
Average period between gestations.....	37	27.9	40.5	28	42
Number of days in which these data were obtained†	(210-300) 259	(80-300) 170	(30-230) 164	(55-201) 120	55

* F₁, F₂, etc., refer to the offspring of treated pairs F₀, F₁, etc.

† The figures in parentheses indicate the range of values; the figures in the lower line indicate the average.

TABLE 12.—*Development of Thymus-Treated Rats as Contrasted with Development of Control Animals*

	Control Animals	F ₁	F ₂	F ₃	F ₄
Average weight at birth, Gm.*.....	4.6	5.1	5.3	5.3	5.6
Opening of ears, days.....	2½-3½	2	1-2	1	1
Eruption of teeth, days.....	8-10	1-9	1-2	1	1
Appearance of hair, days.....	12-16	3-12	4-6	4-5	2-3
Opening of eyes, days.....	14-17	12-14	4-6	4-6	2-3
Descent of testes, days.....	35-40	15-29†	5-21†	5-12†	4-5
Opening of vagina, days.....	55-62	30-45†	23-32†	21-27†	18-19

* These figures are based on 103 animals in the control series and 124 in the F₁, 115 in the F₂, 76 in the F₃ and 21 in the F₄ generation.

† The low numbers usually relate to late litters in the generation and the high numbers to the first litters born.

In addition to these biologic effects there are other manifestations which have not been so well emphasized. These include behaviorism, psychic attributes, the effects on the circulatory system, the fertility of treated females, the influence on test offspring of nursing by control mothers and the effect of thymus extract on new-born rats.

The psychic precocity is as striking as the physical in the thymus-treated strain of rats. Thus fifth generation test animals moved about the cage at 3 days of age and appeared as capable and alert as normal rats of from 16 to 20 days of age. Such animals are able to climb out of a wire net enclosure from 3 to 4 inches high.

and paravertebral zone. Macklin²⁴ also called particular attention to the marked limitation of expansile movements in the posterior paravertebral region which lies above and behind the hilus almost completely surrounded by the rigid structures of the thorax. The area designated by Macklin as the superoretroradicular region coincides closely with that defined by Tendeloo. It is thus evident that the area in question includes a considerably larger portion than the apex of the upper lobe. Tendeloo regarded the fifth rib as its inferior boundary, which makes it practically identical with Macklin's superoretroradicular region. It is of particular significance to point out here that both these authors stressed the fact that the apex of the lower lobe forms a part of this zone.

It appears, therefore, that the region particularly prone to tuberculous involvement includes the posterior aspect of the upper lobe and the apex of the lower lobe. That the dorsal portion of the upper lobe represents the most common location of the initial changes is borne out by roentgenologic studies of early cases, as well as by observations at necropsy. This was long ago clearly demonstrated by Birch-Hirschfeld²⁵ and more recently again emphasized by Loeschcke.²⁶ Assmann¹⁵ pointed out that the location of the infraclavicular infiltrates corresponds with the dorsal subapical region of the upper lobe, and Sweany, Cook and Kegerreis¹⁶ recently called attention to the posterior location of nearly all early cavities. The apex of the lower lobe, however, represents a comparatively infrequent location of early lesions, if taken by and large in relation with the frequency of involvement of the upper lobe. It seems, therefore, that, generally speaking, there is a better chance for the apex of the lower lobe to escape involvement, and that the operation of certain additional factors may be necessary in order to bring about the development of a lesion in that location.

What are the conditions that may enhance the susceptibility of this region of the lung? It is important to recall here that the lower lobe and the dorsal portion of the upper lobe are expanded mainly by the diaphragmatic movements, in contrast to the greater portion of the upper lobe (on the right side also the middle lobe), which is acted on by the costal mechanism (Keith²⁷). The action of the diaphragm, however, is exerted chiefly on the caudal and lateral portions of the lung and decreases progressively in the direction from the base toward

24. Macklin, C. C.: The Dynamic Bronchial Tree, *Am. Rev. Tuberc.* **25**:393 (March) 1932; Bronchial Length Changes and Other Movements, *Tubercle* **14**: 16 and 69, 1933.

25. Birch-Hirschfeld, F. V.: Ueber den Sitz und die Entwicklung der primären Lungentuberkulose, *Deutsches Arch. f. klin. Med.* **64**:58, 1899.

26. Loeschcke, H.: Ueber das Wesen der Lungenspitzen disposition zur Tuberkulose-Erkrankung, *Beitr. z. Klin. d. Tuberk.* **64**:344, 1926.

27. Keith, A.: The Mechanism of Respiration in Man, in Hill, Leonard: *Further Advances in Physiology*, New York, Longmans, Green & Co., 1909.

Weaning is possible at 3 days of age, the rats finding their water, milk and food supply. They burrow under the excelsior, find a resting place and have no need of further care from the parents.

The thymus-treated animals appear to be in good health, and their reactions asleep or awake resemble in all respects those of normal rats. They are entirely docile and easily handled without gloves. They do not resent puncture with the needle to any great extent and apparently suffer no pain or distress following the injection of thymus extract. We have wondered at times whether the chlorbutanol used as a preservative in this extract in any way accounts for the docility observed.

White rats swim instinctively. Young rats can swim as soon as their eyes open and they are covered with fur. Our third generation rats swam at the age of 6 and 7 days; our fourth generation rats at 4 and 5 days, and our fifth generation rats at from 3 to 4 days. None of these animals entered the water voluntarily, but when thrown into water they appeared at a loss only momentarily and then swam toward the nearest shore. They swam rapidly with their heads well up out of the water. If the water was not too deep, they stood on their hindlegs and made frantic efforts to spring to safety. The control rats could not swim until after the eyes opened, i. e., until from 14 to 16 days of age.

With the amounts of medication employed in these experiments little or no effect can be noted on the circulation of the rat. However, when given in large or toxic doses to either dogs or rats thymus extract exercises a profound effect on the cardiovascular system. Thus in dogs attached to the kymograph the blood pressure fell 14 mm. following an injection of 1 cc., and following an injection of 40 cc. it fell 66 mm. and persisted at this level for sixteen minutes. Electrocardiographic tracings were made for rats in several instances in conjunction with Dr. T. A. McMillan and Dr. Samuel Bellet of the Philadelphia General Hospital. Needles inserted into the muscles of the extremities constituted the electrical contacts. It was found that thymus extract (Hanson) in doses of 1 cc. exercised little or no effect. However, following intraperitoneal administration of 5 cc., cardiac arrhythmia developed, ending eventually in auriculoventricular dissociation and complete heart block.

The period between the casting of litters has varied slightly in both control and test animals. However, the averages for each group are of considerable interest. The average time between litters for the control animals has been thirty-seven days, whereas for treated parents it was twenty-seven and nine-tenths days in the F_1 , forty and five-tenths days in the F_2 , twenty-eight days in the F_3 , and forty-two days in the F_4 generation.

represent a distinct part of the vulnerable zone, though to a lesser degree than the upper lobe. It is thus perhaps merely a matter of accident if this portion becomes involved in preference to more common locations. It cannot be denied, however, that additional factors, such as an increase of the infective dose beyond a certain threshold or a diminished state of resistance, may be necessary in order to produce changes in this ordinarily less susceptible region of the lung.

A further point which supports the conception just outlined is the fact that in some cases of this group the lesion developed during the course of pregnancy. Although this combination was present in only a few instances, it nevertheless deserves attention, considering the rather infrequent occurrence of lesions of the lower lobe in general. It is also of interest to note that among the very few cases of initial involvement of the lower lobe recorded from postmortem observations there were two instances which concerned pregnant women (Birch-Hirschfeld²⁵ and Beitzke³⁰). The elevation of the diaphragm and its restricted movements on quiet breathing which take place in pregnancy cause impaired ventilation of the lower lobe, which is especially pronounced in its apical area, thus accentuating the already preexisting unfavorable conditions in women. An additional factor which may also have some effect is a relaxation of the tension exerted by the diaphragm on the summit of the lung (Orsós³¹) as a result of increased intra-abdominal pressure. The combination of these factors is apt to favor a downward shift of the predisposed zone.

Another significant finding which seems to point in the same direction is the predominance of lesions of the lower lobe on the right side. This is striking in view of the fact that there is no definite preference for the right side in the reinfection forms of pulmonary tuberculosis as a whole. It is possible that the higher position and more limited excursions of the right side of the diaphragm may operate as contributing factors. There is also a possibility that the anatomic course of the right main bronchus, which runs in a more straight line in relation to the trachea, may to a certain extent favor an aerogenous infection of the right lung. In this respect the lesions of the lower lobe show a certain parallel with the primary infection, which also seems to have a preference for the right lung (Pagel and Henke³² and Stoloff³³).

30. Beitzke, H.: *Pathologische Anatomie der Lungentuberkulose im Pubertätsalter*, *Ergebn. d. ges. Tuberk.* **3**:1, 1931.

31. Orsós, F.: *Die generelle mechanische Disposition der Lungenkuppen zur Tuberkulose*, *Beitr. z. Klin. d. Tuberk.* **70**:504, 1928.

32. Pagel, W., and Henke, F.: *Lungentuberkulose*, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1930, vol. 3, pt. 2.

33. Stoloff, E. G.: *Primary Infection in Tuberculosis*, *Am. J. Dis. Child.* **33**: 363 (March) 1927.

New-born rats of the thymus-treated group removed from their mothers¹³ and placed with control "wet nurse" rats evidenced precocity comparable to that of litter mates left with thymus-treated parents. This experiment was carried out in several instances in which the litter was too large or poorly fed because of lack of milk or neglect on the part of the mother. Control new-born rats suckled by mothers treated with thymus extract whose litters had evidenced marked precocity manifested no precocity and no increase in the rate of growth and development.

Thymus extract was injected into the new-born control young in several instances; as a rule, no effect was noted during the early stage of growth and development. However, in one group which had received injections the eyes opened prematurely on the tenth day. Injection of thymus extract had no effect whatever on the weight curve, the weight of animals receiving injections corresponding throughout to that of their litter mate controls.

The mortality in the F_1 treated generation was 42 per cent, calculated on 2 litters; in the F_2 , 27 per cent; in the F_3 , 40 per cent, and in the F_4 , 43 per cent. In many instances the rats died owing to lack of milk. The average mortality for the entire thymus-treated group was 38 per cent, while that for the control group was 62.2 per cent from July 9, 1933, to April 16, 1934. This vast difference may possibly be accounted for by the increased number of thymus-treated parents breeding as compared to the control animals.

SUMMARY

The thymus extract prepared from the thymus glands of young calves by Hanson and forwarded to us by him is active. All thymus extracts made by Hanson's method, however, are not equally potent, as evidenced by one preparation submitted from another source.

When injected intraperitoneally, Hanson's extract seems to increase the weight and growth of prepubertal male and of mated mature female rats, but it exerts no noticeable effect on the new-born animals.

Treatment of parent rats seems to increase slightly the number and size of the litters and the weight of the young at birth. The most striking biologic effects are observed in the offspring of successive generations of rats continuously treated by intraperitoneal injection and consist of accruing acceleration in growth and development, namely, early eruption of teeth, appearance of fur, opening of the eyes, descent of the testes and opening of the vagina. While precocity was lacking

13. Studies are being made to determine whether the treatment of the mothers alone or of the fathers alone will result in precocity or whether treatment of both parents is necessary.

rendering differentiation from other chronic pulmonary lesions at times difficult. However, purely basal locations without involvement of other portions of the lung are extremely rare. On the other hand, a tuberculous lesion involving the apex of the lower lobe or a massive process of the lower lobe seldom offers serious differential diagnostic difficulties, as these conditions almost invariably present features of the progressive and caseous-cavernous forms with tubercle bacilli in the sputum.

Occasionally, if the patient is seen in the early phase of the disease before any breaking down has taken place, the possibility of nontuberculous bronchopneumonia, as it occurs in grip, may have to be entertained for a while, especially since the onset may be similar in both conditions. More from the roentgenologic than from the clinical standpoint the possibility of neoplasm or abscess may also have to be considered, the former because of the apparent proximity of tuberculosis of the lower lobe to the area of the root, the latter in cases in which there is a solitary cavity with collection of fluid and no other changes in the vicinity. However, only exceptionally will real difficulties arise if all the available clinical and roentgenologic data have been properly evaluated. Of paramount importance is, of course, a careful search of the sputum for tubercle bacilli, no matter how unusual or atypical the location of the process may seem.³⁷

SUMMARY AND CONCLUSIONS

The subject of pulmonary tuberculosis of the lower lobe in adults is presented with particular attention to the early reinfection changes occurring in that location.

Strictly basal tuberculosis must be differentiated from lesions involving the superior portion of the lower lobe. Early changes limited to the base of the lung are extremely rare, whereas the apical and sub-apical regions of the lower lobe represent a typical site of predilection for initial manifestations in the adult form of phthisis. This area is also a fairly frequent location of early bronchogenous metastases in progressive tuberculosis of the upper lobe.

The tuberculous changes occurring in the apex of the lower lobe are almost invariably of the exudative and caseous type, with early cavity formation. Collapse therapy is the only effective treatment, and

37. Since this paper was submitted for publication, twenty-two additional cases of tuberculosis of the lower lobe could be observed. This brings up the total number of patients of this series to fifty-six. Of these, forty-five were females and eleven were males. Among the additional five male patients, two had diabetes and in one patient there was a combination with silicosis. In the additional group of seventeen female patients, there were two instances of diabetes. The ratio between males and females based on the total series shows no material change, as compared with the results originally obtained.

in the early litters born of thymus-treated parents in the first generation, it appeared in later litters. This precocity is apparently not effected through the mother's milk. Young rats from thymus-treated strains occasionally matured and bred early when they received injections of thymus extract or not, as both thymus-treated and control rats in the F_1 generation cast litters at forty-two and forty-five days, respectively (rats 62 and 63 and rats 64 and 65). Judging from our experiments, then, it appears that thymus extract (Hanson) affects the fertility and rate of growth and development of white rats.

Interruption of thymus administration for one generation nullified to a large extent the effects of the previous administration of thymus even though the treatment may have extended through several generations of rats.

Rats receiving thymus extract appear unusually docile, healthy and contented.

Excessive amounts of thymus extract result in toxicity, as evidenced by increasing auriculoventricular dissociation and eventual heart block.

CONCLUSIONS

1. Thymus extract (Hanson) has accelerated the rate of growth and development, hastened the onset of adolescence in the offspring of treated rats and increased the fertility of parent rats.

2. This acceleration may be noted in later litters of the second generation but is more marked in each succeeding generation under treatment.

3. The treatment of succeeding generations of parent rats with injections of thymus extract has resulted in the amplification of the effects of thymus extract and has possibly thrown some light on the rôle of the thymus gland.¹⁴

14. Since this paper was submitted for publication, our attention has been drawn to the section, "Entwicklung und Wachstum" by F. Gudernatsch in Hirsch, Max: *Handbuch der inneren Sekretion*, Leipzig, Curt Kabitzsch, 1930. Between 1912 and 1919 Gudernatsch administered dried endocrine glands to successive generations of white rats. Treatment was begun as soon as the nursing period was passed. Gudernatsch observed that the feeding of dried thymus gland brought about the following results: healthy animals, numerous pregnancies, large litters, long life and other biologic changes.

STAB WOUNDS OF THE HEART

A STUDY OF ELECTROCARDIOGRAPHIC CHANGES, POLYSEROSITIS
(PICK'S SYNDROME) AND PERICARDITIS

JOHN D. KOUCKY, M.D.

AND

GEORGE MILLES, M.D.

CHICAGO

Since the report of the first case by Cappelen in 1895 and that of the first case with recovery by Rehn in 1896,¹ innumerable instances of surgical repair of wounds of the heart have been recorded. Indeed, this life-saving procedure has become so commonplace that reports of cases limited to the surgical aspects add little to the literature on the subject which Lockwood² reviewed exhaustively. This case is reported because it presents certain features which are worthy of study. In the first place, a series of electrocardiograms was obtained, and as relatively few electrocardiographic studies have been made in cases of wounds of the heart, a summary and comparison of all such reports appear to be of value. Second, the case is of interest in that it serves to substantiate and elucidate further the findings of Beck³ and his co-workers in experimental studies of Pick's syndrome in dogs. Finally, it is a case in which life was so close to being extinct that the entire surgical procedure, including the subsequent cutting down on the veins for the injection of saline solution and for transfusion, was performed without either local or general anesthesia.

REPORT OF A CASE

E. G., a 16 year old white boy, was carried into the Lutheran Deaconess Hospital at 10:50 p. m. with a history of having been stabbed with a pocket-knife about ten minutes previously, after which injury he ran about 75 yards and collapsed.

He was in a comatose condition; his lips were faintly cyanotic; his skin was pale, cold and clammy; he was gasping, and his clothes were soaked with blood.

From the Departments of Surgery and Pathology of the University of Illinois College of Medicine, and the Lutheran Deaconess Hospital.

1. Schmidt-Weyland¹² reported his observations in 1931 in a case of surgical repair of a gunshot wound self-inflicted in 1895.

2. Lockwood, A. L.: Surgery of the Pericardium and Heart, Arch. Surg. **18**:417 (Jan., pt. 1) 1929.

3. (a) Beck, C. S.: The Effect of Surgical Solution of Chlorinated Soda (Dakin's Solution) in the Pericardial Cavity, Arch. Surg. **18**:1659 (April, pt. 2) 1929. (b) Beck, C. D., and Griswold, R. A.: Pericardiectomy in the Treatment of the Pick Syndrome, *ibid.* **21**:1064 (Dec.) 1930.

COST OF WORK IN PATIENTS WITH HYPERMETABOLISM DUE TO LEUKEMIA AND TO EXOPHTHALMIC GOITER

STELLA PAISLEY BRIARD, M.S.

J. T. McCLINTOCK, M.D.

AND

C. W. BALDRIDGE, M.D.†

IOWA CITY

A similarity between exophthalmic goiter and leukemia, especially as regards the ratio of the basal metabolic rate to the basal pulse rate, has been pointed out by Minot and Means.¹ Friedgood² reported that a response to compound solution of iodine similar to that seen in patients with exophthalmic goiter was obtained in six of ten patients with lymphatic leukemia. Both of these communications contain further comment on the similarities of the two conditions. Recently Dameshek, Berlin and Blumgart³ have reported a case of chronic lymphatic leukemia (aleukemic) in which total ablation of the thyroid gland resulted in considerable clinical and hematologic improvement.

We have been more interested in the fundamental differences between exophthalmic goiter and leukemia than in their similarities. We have reported investigations⁴ which show that protein catabolism is an important factor in the production of hypermetabolism in the common blood dyscrasias. One difference between exophthalmic goiter

† Dr. Baldrige died Nov. 22, 1934.

From the Departments of Physiology and Internal Medicine, State University of Iowa College of Medicine.

1. Minot, G. R., and Means, J. H.: The Metabolism-Pulse Ratio in Exophthalmic Goiter and in Leukemia, *Arch. Int. Med.* **33**:576 (May) 1924.

2. Friedgood, H. B.: The Effect of Lugol's Solution on Chronic Lymphatic Leukemia and Its Bearing on the Pathogenesis of Exophthalmic Goiter, *Am. J. M. Sc.* **183**:515 (April) 1932.

3. Dameshek, W.; Berlin, D. O., and Blumgart, H. L.: Complete Ablation of the Thyroid Gland in a Case of Chronic Lymphatic Leukemia with Hypermetabolism, *New England J. Med.* **210**:723 (April 5) 1934.

4. Baldrige, C. W., and Barer, A.: Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism: I. In Pernicious Anemia, *J. Clin. Investigation* **10**:529 (Aug.) 1931; Relationship Between Oxygen Consumption and Nitrogen Metabolism: II. In Leukemia, *Arch. Int. Med.* **51**:589 (April) 1933. Barer, A.; Paul, W. D., and Baldrige, C. W.: Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism: III. In Polycythemia Vera, *J. Clin. Investigation* **13**:15 (Jan.) 1934.

maximum daily fluctuation to 101 F. occurred. Serous drainage from the pericardial sac had gradually diminished, and the size of the opening into the sac was now 1 cm. in diameter.

During the eighth week, without any treatment directed to the cardiac condition or the anasarca, a sudden dramatic change occurred. The urinary output increased to a point at which it daily exceeded the intake of fluid by from 1,000 to 1,500 cc. The evidences of toxemia disappeared; the pulse became full and gradually dropped to the normal rate, and the abdominal and pleural fluids vanished. The pericardial discharge by this time had also become small in amount.

Three weeks after the onset of this sudden improvement and seventy days after operation, the patient had recovered sufficiently to walk out of the hospital with the wound healed. Repeated examinations since that time failed to reveal any abnormal cardiac findings, except apparent adherence of the heart to the overlying scar with retraction of the scar at each heart beat. Cardiac reserve appears to be unembarrassed, and the patient has regained his normal weight, with a total increase of 30 pounds (13.6 Kg.), two months after leaving the hospital and five months after his injury.

ELECTROCARDIOGRAPHIC STUDIES

Cole⁴ reported apparently the first case of stab wound of the left ventricle with surgical treatment followed by recovery in which electrocardiograms were made. A single tracing (fig. 3 C) made six weeks after the injury was practically normal.

In the case reported by Davenport⁵ the wound, 5 mm. in diameter, was in the upper portion of the middle third of the right ventricle, 3 mm. from the anterior descending branch of the left coronary artery. The anterior descending branch of the left coronary artery was ligated in the course of the operation (fig. 4 B). An inverted T wave persisted in all leads until the fifty-ninth day. Except for a rather low potential, the tracing was normal on the two hundred and fifty-seventh day.

Bates and Talley⁶ reported a case of stab wound in the left ventricle. During operation the heart stopped, but cardiac action was restored by massage. A friction rub developed after ten days, and the cardiac shadow was considerably enlarged to the left on the eleventh day but was again normal in size on the twenty-sixth day. The patient was discharged symptom-free twenty-six days after his admission (fig. 5 A). A high take-off was recorded for the T wave in leads I and II. The T wave lead III was inverted on the fifth day. By the twentieth day the Pardee curve had been replaced by an inverted T wave in all three leads, which persisted until the ninetieth day. The T wave in lead III was still inverted on the hundred and thirty-second day. The R wave in that lead was irregularly notched in all tracings until, and including, the one taken on the ninetieth day.

4. Cole, D. B.: *Ann. Surg.* **85**:647, 1921.

5. Davenport, G.: *Suture of Wound of the Heart*, *J. A. M. A.* **82**:1840 (June 7) 1924.

6. Bates, W., and Talley, J. E.: *Am. Heart J.* **5**:232, 1929.

and leukemia has impressed us. It is well known that after some experience one is able to estimate the basal metabolic rate of a patient with exophthalmic goiter with considerable accuracy by considering the clinical evidences of consumption of fuel, production of heat and circulatory changes incident to increased minute volume flow of blood. By using the same criteria our attempts to estimate the metabolic rate of patients with leukemia prove to be most erratic. Neither the loss of weight nor the increase in appetite appears to be as regular or as marked in patients with leukemia as in patients with exophthalmic goiter even though the degree of hypermetabolism is comparable.

Plummer and Boothby,⁵ as well as Smith,⁶ have demonstrated that patients with exophthalmic goiter work much less efficiently than normal persons. We now wish to report studies in which we compared the efficiency of patients with exophthalmic goiter with that of patients with a similar degree of hypermetabolism due to leukemia.

METHOD

The patient was up and about the ward for at least three days before the tests were made. During this time the patient was put on the treadmill in order that he might become accustomed to it and in order to determine the speed at which he could walk without exhaustion (usually 60 to 70 meters per minute). On the morning of the test the patient, in the postabsorptive state, was taken to the laboratory on a cart. He stood quietly on the treadmill for five minutes during which time the expired air was collected in the first of four Douglas bags by means of an orinasa mask. The air expired during the five minute walking period was collected in bag 2. The expired air was also collected in separate bags during a third and a fourth five minute period. The volume of gas in each bag was measured by a wet gas meter, and the analysis was made with the Haldane apparatus. The metabolism while standing was determined from the first five minute period. The total increase in consumption of oxygen during the periods of walking and of recovery was considered to represent the oxygen required for walking. The number of steps was recorded on a kymograph, and a "work adder" measured the total amount of elevation of the body during walking. The treadmill was similar to that described by Benedict and Murschausen.⁷

The metabolism while standing was used as a basis for determining the cost of walking. For purposes of comparison, values are given in gram calories used in moving 1 Kg. 1 meter horizontally. Although the actual amount of energy necessary to raise and lower the body has been calculated, no attempt has been made to separate this factor from the total energy used in walking as far as tables 1 and 2 are concerned. The theoretical normal has been calculated according to

5. Plummer, H. S., and Boothby, W. M.: The Cost of Work in Exophthalmic Goiter, *Am. J. Physiol.* **63**:406, 1923.

6. Smith, J. H.: Basal Metabolism: III. Influence of Work with Special Reference to the Thyroid Gland, *Arch. Int. Med.* **42**:47 (July) 1928.

7. Benedict, F. G., and Murschausen, H.: Energy Transformations During Horizontal Walking, Publ. no. 231, Carnegie Institution of Washington, 1915, p. 34.

the sixteenth day the T wave in leads I and II was diphasic, and on the seventy-sixth day it was inverted in lead I and upright in leads II and III.

Porter and Bigger¹⁰ reported two cases with electrocardiograms. In the first case the wound, 1 cm. in length, was in the left ventricle and divided the posterior descending branch of the left coronary artery. The wound was repaired, and the coronary artery was ligated. The electrocardiogram (fig. 4 A) showed a high take-off on the first day which persisted till, and including, the sixth day. It was replaced on the sixteenth day by an inverted T wave which became upright on the sixty-second day.

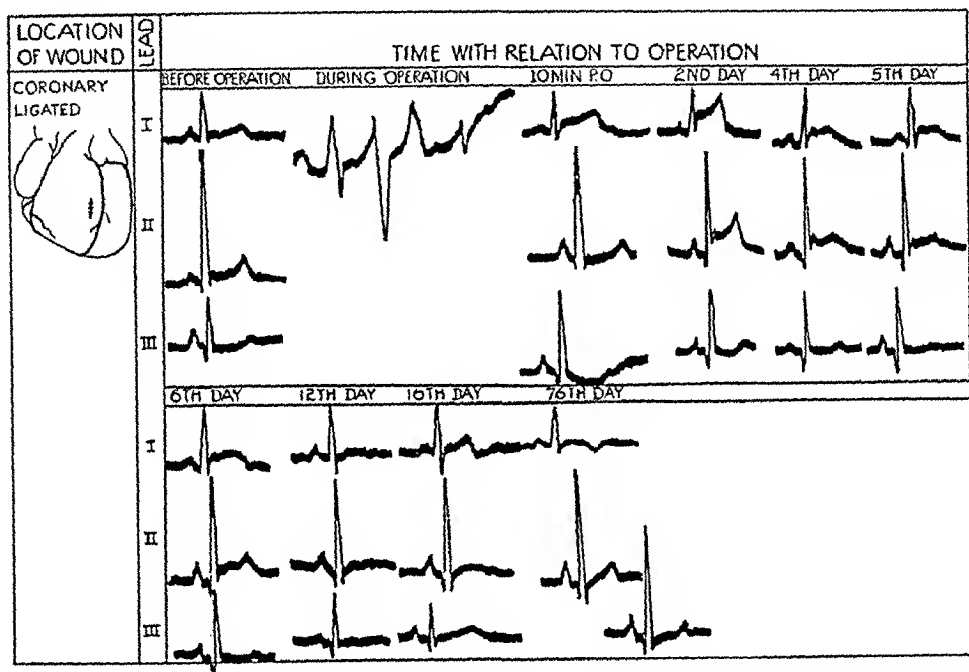


Fig. 7.—Diagram showing location of the wound and electrocardiograms obtained in the case of Purks (tracings taken from Purks¹⁰).

In the second case the stab wound was in the right ventricle and did not involve the coronary arteries. The electrocardiograms (fig. 3 A) were characterized by a low potential in lead I, a large T wave in leads II and III with a high take-off on the first day and a high take-off in all leads on the second day, which persisted through the ninth day. On the nineteenth day the T wave was inverted in leads I and II and was diphasic in lead III. On the thirty-third and fifty-fifth days the T wave was inverted in all leads, and on the seventy-third day, except for a low potential in lead I, the curve was normal.

Both operations were performed with the patients under local anesthesia. Neither pain nor other symptoms were complained of at any

10. Porter, W. B., and Bigger, I. A.: *Am. J. M. Sc.* 184:799, 1932.

the method of McClintock and Paisley.⁸ The cost of transporting 1 Kg. 1 meter horizontally has been considered to be 0.538 calories⁹ for men from 25 to 29 years of age and 0.52 for women of the same age. The latter figure is an average of the results given by Smith and Doolittle¹⁰ in their table 4.

RESULTS

In two patients with leukemia the basal metabolic rate was definitely within normal limits. The patient E. A. was tested on two occasions about six months apart, and during the second test period her average basal metabolic rate was only 5 per cent above normal. Comparisons will be based on the average results in eleven patients with leukemia and eight patients with hyperthyroidism, in all of whom there was hypermetabolism. The average basal metabolic rate in the patients with leukemia was 38 per cent above normal while that of the patients with hyperthyroidism was increased 40 per cent. Eight of the eleven patients with leukemia were men, while all of the patients with hyperthyroidism were women. The patients with leukemia averaged almost 15 years older than those of the other group.

In all patients the respiratory metabolism was determined in the postabsorptive state. In the patients with leukemia the metabolism while standing was about 18 per cent higher than the true basal metabolism, while in the patients with hyperthyroidism the difference amounted to 23 per cent. Only three of the patients, all of whom had leukemia, had been confined to bed for any appreciable time before the tests were made. These three patients (G. A., J. R. and G. N.) walked about the ward three days before the tests were made, but even so the increase in metabolism incident to standing averaged about 32 per cent of the basal rate, whereas in the other eight subjects the increase was only 11 per cent. The latter figure is comparable to the 12 per cent increase in normal subjects reported by Smith.¹¹

Tables 1 and 2 indicate that the cost of work in the patients with hyperthyroidism averaged about 38 per cent above the calculated normal, while in patients with leukemia the corresponding figure was 8.5 per cent below normal. Marked as this difference is it does not represent the whole picture. The cost of work was determined with the metabolism while standing as a base-line, and the metabolism while standing was 5 per cent lower in the patients with leukemia than in those with

8. McClintock, J. T., and Paisley, S.: Cost of Work in Relation to Basal Metabolism, *Proc. Soc. Exper. Biol. & Med.* **30**:162 (Nov.) 1932.

9. Smith, H. M.: Gaseous Exchange and Physiological Requirements for Level and Grade Walking, Publ. no. 309, Carnegie Institution of Washington, 1922, p. 143.

10. Smith, H. M., and Doolittle, D. B.: Energy Expenditure of Women During Walking at Different Speeds, *J. Biol. Chem.* **65**:665 (Oct.) 1925.

11. Smith,⁹ p. 101.

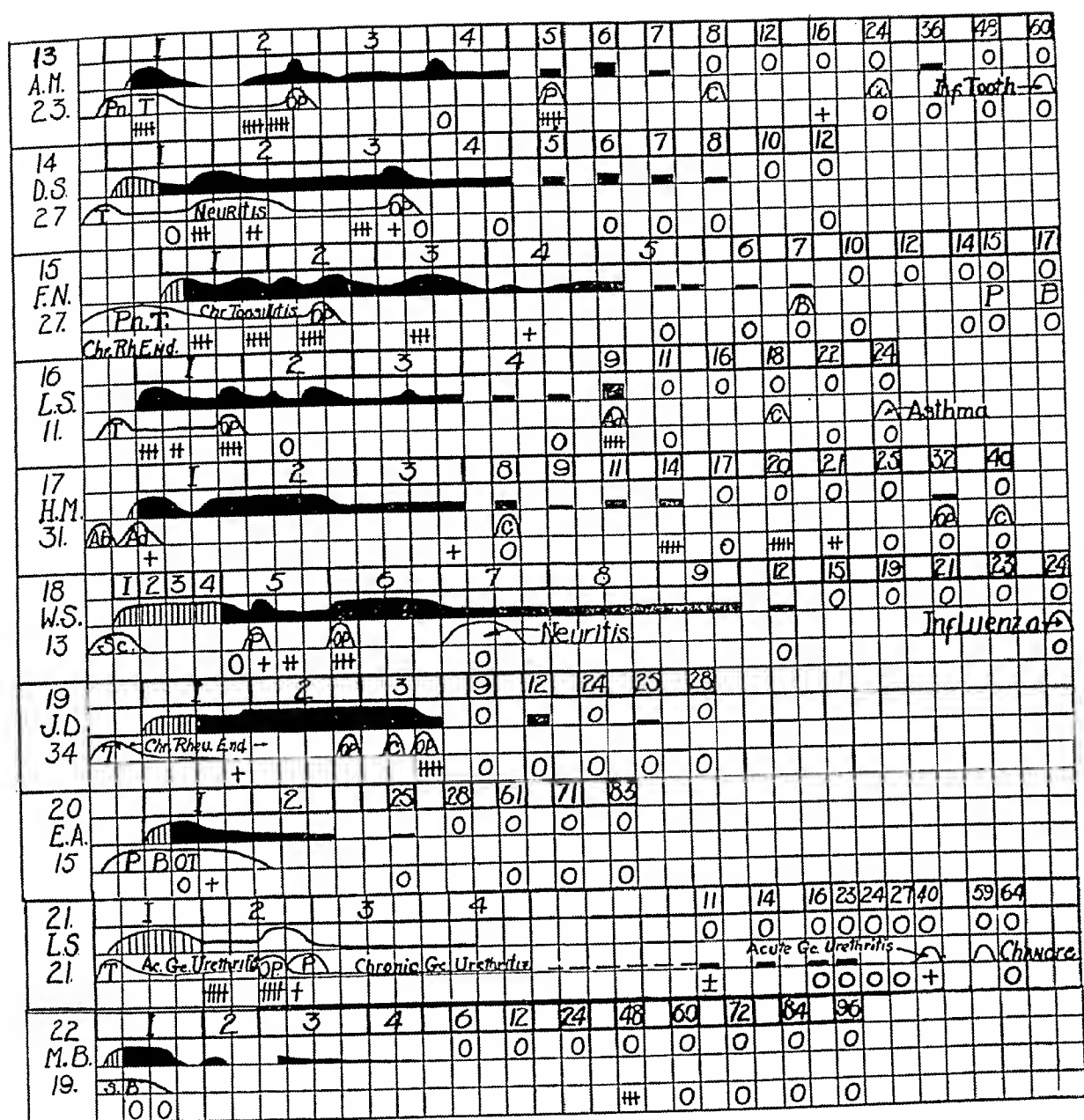


Chart 1.—Part 2.

Chart 1.—Well group. In cases 1 to 21 hemorrhagic nephritis had been associated with the presence of *Str. haemolyticus*, beta type. In case 22, microorganisms had not been demonstrated to be present.

In charts 1, 2 and 3 four lines have been allotted to each case, representing in order, from top to bottom, the month of the onset of the disease, the general progress of the disease (cross-hatching indicates that prior to our observations; black, that thereafter), the infections observed and the presence or absence of *Str. haemolyticus*, designated as + or 0, respectively. In the left hand margin are given in order from top to bottom the number of the cases and the initials and age of the patient.

The following abbreviations are employed in the charts: *A*, appendicitis; *Ab*, abscess; *Ad*, adenitis; *B*, bronchitis; *C*, coryza; *D*, dead; *Ery*, erythema; *Gc*, gonorrheal urethritis; *I*, influenza; *M*, measles; *Op*, operation (usually tonsillectomy and adenoidectomy); *P*, pharyngitis; *Pn*, pneumonia; *S*, sinusitis; *Sc*, scarlet fever; *T*, tonsillitis; *V*, varicella.

*Denny, E. R., and Baker, B. M., Jr.: Varicella Complicated by Acute Nephritis, *Bull. Johns Hopkins Hosp.* 44:201, 1929.

hyperthyroidism. On the average the patients with leukemia did 26 per cent more kilogram-meters of work in raising and lowering their bodies than was done by the patients with hyperthyroidism. The relationship between the basal metabolism and the cost of walking has been estab-

TABLE 1.—*The Cost of Work in Patients with Leukemia*

Subject	Age, Years	Sex	Average Basal Metabolic Rate, Per- centage	Gram Calories per Kg. = M.		Devia- tion, Per- centage	Respiratory Quotient		Kind of Leukemia
				Calcu- lated Normal	Deter- mined		Stand- ing	Walking and Recovery	
E. A.	43	F	+ 5	0.502	0.552	+ 9	0.775	0.784	Myelogenous
W. H.	58	M	+11	0.489	0.534	+ 9	0.802	0.754	Lymphatic
G. A.	46	M	+13	0.505	0.359	-21	0.756	0.833	Myelogenous
T. N.	73	M	+26	0.465	0.427	- 8	0.788	0.831	Myelogenous
H. W.	62	M	+27	0.481	0.396	-19	0.803	0.867	Lymphatic
E. G.	41	F	+29	0.502	0.560	+12	0.708	0.742	Myelogenous
E. A.	43	F	+35	0.502	0.516	+ 3	0.785	0.780	Myelogenous
S. S.	53	M	+42	0.494	0.413	-16	0.736	0.731	Lymphatic
N. E.	51	F	+44	0.490	0.517	+ 5	0.691	0.769	Myelogenous
L. C.	41	M	+45	0.511	0.343	-33	0.690	0.725	Myelogenous
J. R.	60	M	+49	0.481	0.525	+ 9	0.728	0.780	Lymphatic
R. E.	38	M	+52	0.511	0.409	-20	0.686	0.734	Myelogenous
G. N.	61	M	+57	0.481	0.454	- 6	0.660	0.699	Lymphoma, lymphoblastic type
Average	52	..	+38	0.493	0.447	- 8.5	0.730	0.774	

TABLE 2.—*The Cost of Work in Patients with Hyperthyroidism, Myxedema and Mitral Stenosis*

Subject	Age, Years	Sex	Average Basal Metabolic Rate, Percentage	Gram Calories per Kg. = M.		Deviation, Percentage	Respiratory Quotient	
				Calcu- lated Normal	Deter- mined		Standing	Walking and Recovery
Hyperthyroidism								
G. F.	44	F	+13	0.497	0.620	+25	0.824	0.831
V. R.	20	F	+21	0.524	0.595	+13	0.805	0.777
T. H.	43	F	+32	0.502	0.759	+51	0.784	0.800
C. J.	38	F	+39	0.509	0.779	+53	0.748	0.774
H. M.	24	F	+42	0.524	0.610	+16	0.709	0.797
V. A.	27	F	+50	0.520	0.789	+52	0.719	0.785
A. V.	53	F	+55	0.490	0.701	+43	0.744	0.807
R. S.	49	F	+67	0.497	0.749	+51	0.736	0.816
Average	37	..	+40	0.508	0.700	+38	0.758	0.798
Myxedema								
L. S.	25	F	-42	0.520	0.423	-19	0.760	0.817
Mitral Stenosis								
J. H.	45	F	- 3	0.497	0.544	+ 9	0.666	0.732
H. W.	27	F	- 3	0.520	0.468	- 6	0.714	0.715

lished by McClintock and Paisley⁸ for children, by Smith⁹ for young men and by Smith and Doolittle¹⁰ for young women. We have assumed that these figures obtain in older persons, and it follows that because of differences in age and sex the patients with leukemia had a calculated efficiency 3 per cent greater than those in the other group. Each of these three circumstances tends to widen the already marked disparity

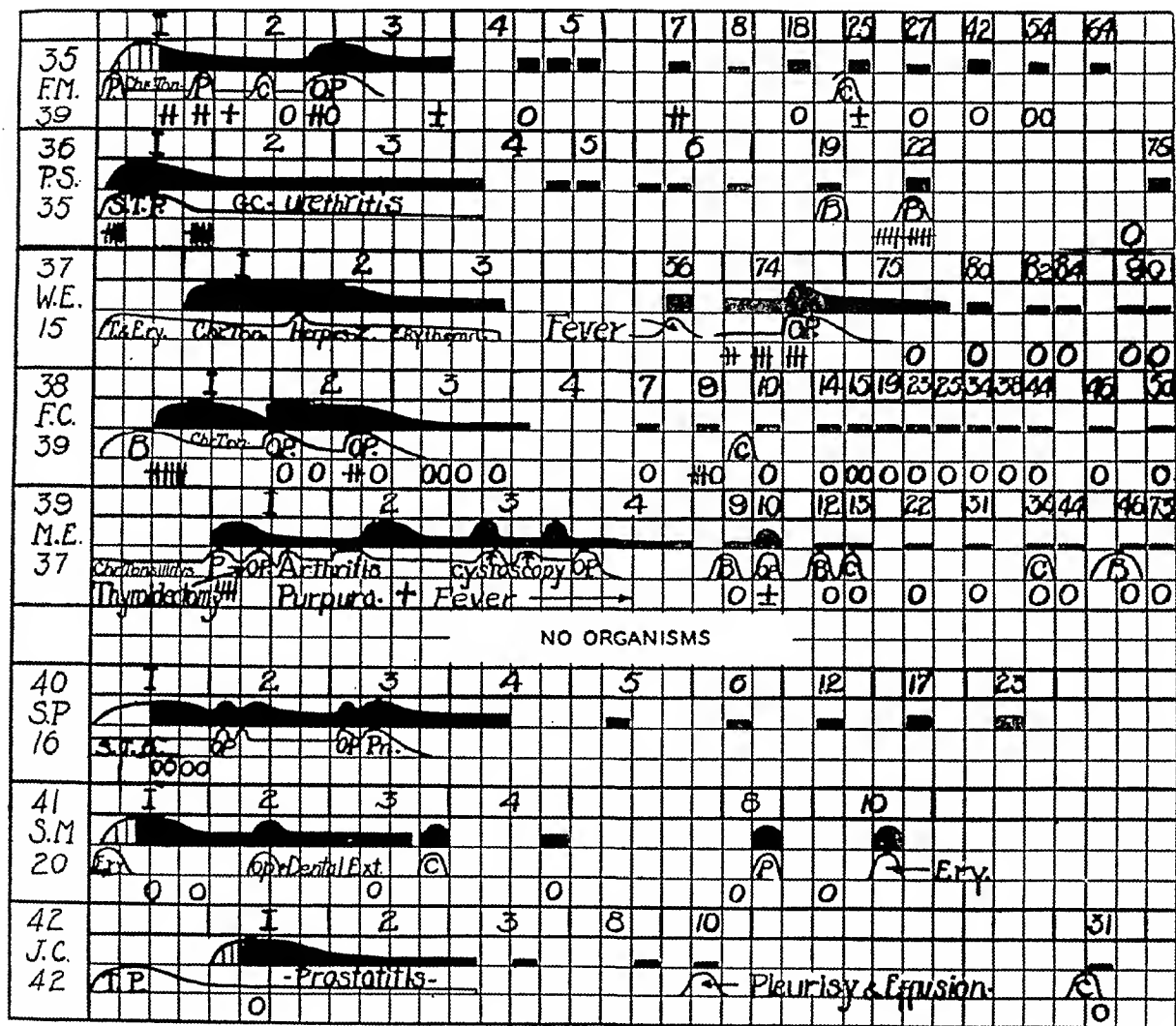


Chart 2.—Part 2.

Chart 2.—Latent group. In cases 23 to 39 hemorrhagic nephritis was associated with the presence of *Str. haemolyticus*. In cases 40 to 42 infection could not be demonstrated.

in the efficiency with which forward progression with its associated movements can be accomplished in these two groups of patients.

The metabolism of the two groups as calculated in calories per square meter per hour is presented in tables 3 and 4. Here again we found a greater increase in the metabolism while standing and walking in the patients with hyperthyroidism than in those with leukemia. In

TABLE 3.—*Metabolism of Patients with Leukemia Calculated in Calories per Square Meter per Hour*

Subject	Calories per Square Meter per Hour				Speed, Meters per Minute	Deviation from Basal Metabolic Rate	
	Normal	Basal	Standing	Walking		Standing	Walking
E. A.	35.3	37.1	43.2	113.6	60.0	+16	+206
W. H.	36.6	40.5	48.2	123.7	73.4	+19	+205
G. A.	37.8	42.9	57.9	104.8	63.4	+35	+144
T. N.	34.8	43.9	43.1	96.3	64.3	- 2	+119
H. W.	36.0	45.6	58.6	112.9	71.4	+28	+147
E. G.	35.3	45.4	54.9	127.6	66.8	+21	+181
E. A.	35.3	47.6	54.3	114.3	65.9	+14	+140
N. E.	34.5	49.6	53.4	113.4	52.1	+ 7	+129
S. S.	37.2	53.1	60.4	120.8	64.6	+13	+127
L. C.	38.3	55.7	57.1	98.1	58.5	+ 2	+ 76
J. R.	36.0	53.6	69.7	135.8	65.6	+30	+153
R. E.	39.2	59.6	70.0	131.7	64.9	+17	+121
G. N.	36.0	56.7	74.2	127.5	55.1	+30	+124
Average.....	36.4	50.3	59.4	116.6	63.0	+18	+133

TABLE 4.—*Metabolism in Patients with Hyperthyroidism, Myxedema and Mitral Stenosis Calculated in Calories per Square Meter per Hour*

Subject	Calories per Square Meter per Hour				Speed, Meters per Minute	Deviation from Basal Metabolite Rate	
	Normal	Basal	Standing	Walking		Standing	Walking
			Hyperthyroidism				
G. F.	35.3	39.9	48.1	125.5	64.7	+21	+215
V. R.	36.9	44.5	47.1	113.7	70.2	+ 6	+156
T. H.	35.3	46.6	71.9	169.6	59.0	+54	+264
C. J.	35.8	49.9	59.2	149.0	65.4	+19	+199
H. M.	36.9	52.3	64.6	153.1	70.8	+24	+193
V. A.	36.6	55.0	62.6	129.5	52.5	+12	+135
A. B.	34.5	53.4	64.5	144.8	66.0	+21	+171
R. S.	35.0	58.3	73.3	160.7	66.1	+26	+158
Average.....	35.8	50.0	61.4	143.2	64.3	+23	+186
Myxedema							
L. S.	36.6	21.2	29.1	70.0	57.0	+37	+230
Mitral Stenosis							
J. H.	35.0	34.0	45.0	119.0	69.2	+32	+250
H. W.	36.6	35.2	44.5	104.4	69.4	+26	+197

the tables the calculated normal is included because of the variations dependent on age and sex. The metabolism while walking was determined during five minutes of actual walking and does not take into account the oxygen debt. In the patients with hyperthyroidism the metabolism while walking was about 186 per cent higher than the determined basal metabolism while in the patients with leukemia it was 133 per cent higher.

It would be interesting to know whether compound solution of iodine affects only the metabolism while resting in patients with hyperthyroidism or whether it also brings about an increase in the efficiency with which work can be done. The patient V. R., who walked more efficiently than any other subject with hyperthyroidism, had a nodular goiter for years and showed symptoms of hypermetabolism after taking iodine. Most of the patients with hyperthyroidism showed a slight but definite decrease in the cost of work when the tests were repeated on three successive days. This was not true of the other patients, and it is probably related to the nervous instability of the subjects with hyperthyroidism.

The conclusion that some patients with leukemia can convert some of the excess heat which is produced at rest into motion might seem inescapable at first glance. A possible source of this heat which may be converted to kinetic energy is hard to determine. The patients were all in the postabsorptive state when the tests were made. We have previously demonstrated that the specific dynamic effect of catabolized body protein accounts for some of the hypermetabolism seen in the blood dyscrasias. Several investigators have presented data which show that the heat incident to the specific dynamic action of protein cannot be converted to kinetic energy, whereas the specific dynamic effect of carbohydrate is not apparent if absorption takes place during muscular activity. These experimental results have been well summarized by Lusk.¹²

It therefore appears that that part of the hypermetabolism in leukemia which is due to the specific dynamic action of catabolized endogenous protein cannot be converted to energy for muscular movements. While endogenous protein was not involved in any of the experiments cited by Lusk, there is no experimental evidence that endogenous and exogenous protein are in any way dissimilar in their specific dynamic effects. Since the patients were in the postabsorptive state there is no reason to attribute any part of the production of heat to the specific dynamic effect of carbohydrate or fat. Tempting as it is to attribute part of the economy of muscular effort in some patients with leukemia to a conversion of basal heat to kinetic energy it must be admitted that the present evidence is not sufficient to warrant such an explanation. In the patient with myxedema there certainly was no excess of heat while resting which might have been transformed to kinetic energy.

The respiratory quotients were usually higher during walking than during standing. This was true in both groups, although some of the

12. Lusk, G.: *The Science of Nutrition*, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 408.

TREATMENT OF CONGESTIVE HEART FAILURE AND ANGINA PECTORIS BY TOTAL ABLATION OF THE NORMAL THYROID GLAND

XVI. THE SENSITIVITY OF MAN TO EPINEPHRINE INJECTED INTRA- VENOUSLY BEFORE AND AFTER TOTAL THYROIDECTOMY

J. E. F. RISEMAN, M.D.

D. R. GILLIGAN, M.S.

AND

H. L. BLUMGART, M.D.

BOSTON

In an earlier communication which presented the therapeutic results following total ablation of the normal thyroid gland in patients with angina pectoris or congestive failure¹ it was stated that "the manner in which relief is afforded by removal of the thyroid gland probably involves several different, though related, mechanisms. The decreased amount of work by the heart, the decreased metabolism of the heart itself, and the decreased sensitivity to epinephrine are some of the possible factors that are being studied." The purpose of this communication is to present studies of the latter factor, namely, the sensitivity of the cardiovascular system to epinephrine before and after total thyroidectomy. Three aspects of the physiologic action of epinephrine in man have been studied: (1) the sensitivity to epinephrine injected intravenously in patients with normal cardiovascular systems, angina pectoris or chronic heart failure; (2) the sensitivity to epinephrine of patients at various levels of basal metabolism and (3) the rôle played by sensitivity to epinephrine in the improvement which occurs in patients with angina pectoris or chronic cardiac disease following total ablation of the thyroid gland.

Previous studies of the physiologic action of epinephrine have been confined for the most part to experimentation on animals. It has been

This investigation was aided by a grant from the William W. Wellington Memorial Research Fund of the Harvard Medical School.

From the Medical Service and Research Laboratories of the Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

1. Blumgart, H. L.; Riseman, J. E. F.; Davis, D., and Berlin, D. D.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, *Arch. Int. Med.* **52**:165 (Aug.) 1933.

shown² that there are marked differences in the response of various species to a given dose of this drug. For this reason it is difficult to interpret clinical conditions in man on the basis of results of experiments on animals. Furthermore, since angina pectoris and congestive cardiac disease are clinical entities which have no close counterpart in laboratory animals our studies have been limited to observations on man.

In most investigations of the response to injections of epinephrine the drug has been administered intramuscularly or subcutaneously. Under such conditions, however, absorption is irregular,³ and hence the action may vary, particularly since small doses may have an effect strikingly different from that of large doses.⁴ Weinberg,⁵ Cori and Buckwald^{2c} and Weiss⁶ have shown that with proper precautions intravenous administration of epinephrine to human beings is safe and feasible and that the pharmacologic effect is immediate and closely related to the rate of injection.

In view of the considerations just outlined, our studies of the action of epinephrine have been made in man, with solutions of epinephrine of known concentration injected by continuous intravenous drip under accurately controlled conditions.

2. (a) Cori, C. F.; Cori, G. T., and Buckwald, K. W.: The Mechanism of Epinephrine Action: VI. Changes in Blood Sugar, Lactic Acid and Blood Pressure During Continuous Intravenous Injection of Epinephrine, *Am. J. Physiol.* **93**:273, 1930. (b) Cori, C. F., and Cori, G. T.: Absorption of Epinephrine from the Subcutaneous Tissue of the Rat, *Proc. Soc. Exper. Biol. & Med.* **27**:558, 1930. (c) Cori, C. F., and Buckwald, K. W.: Effect of Continuous Intravenous Injection of Epinephrine on the Carbohydrate Metabolism, Basal Metabolism and Vascular System of Normal Men, *Am. J. Physiol.* **95**:71, 1930. (d) Dragstedt, C. A.; Wightman, A. H., and Huffman, F. W.: The Hemodynamic Action of Minimal Effective Doses of Epinephrine in the Unanesthetized Dog, *ibid.* **84**:307, 1928. (e) Trendelenburg, P., and Fleischhauer, K.: Ueber den Einfluss des Zuckerstiches auf die Adrenalinsekretion der Nebennieren, *Ztschr. f. d. ges. exper. Med.* **1**:369, 1913.

3. Luckhardt, A. B., and Koppanyi, T.: Conditions Under Which Subcutaneously Injected Epinephrine Gives a Hemodynamic Effect, *Proc. Soc. Exper. Biol. & Med.* **23**:774, 1926. Lilienthal, H.: Epinephrine: A Method of Prolonging Its Effect in Asthma and the Depression of Shock, *J. A. M. A.* **90**:1192 (April 14) 1928.

4. Moore, B., and Purinton, C. O.: Ueber den Einfluss minimaler Mengen Nebennierenextracts auf den Arteriellen Blutdruck, *Arch. f. d. ges. Physiol.* **81**:483, 1900. Hoskins, R. G., and McClure, C. W.: The Adrenal Glands and Blood Pressure, *Arch. Int. Med.* **10**:343 (Oct.) 1912. Cannon, W. B., and Lyman, H.: The Depressor Effect of Adrenalin on Arterial Pressure, *Am. J. Physiol.* **31**:376, 1913.

5. Weinberg, F.: Die Dosierung des Adrenalins bei der intravenösen Dauerinfusion, *Klin. Wchnschr.* **4**:967, 1925.

6. Weiss, S.: Drugs Used in the Treatment of Cardiovascular Diseases: I. Epinephrine and Ephedrine Groups, *Mod. Concepts Cardiovascular Dis.* **3**:3, 1934.

METHODS AND SUBJECTS

The solution of epinephrine used for intravenous administration was freshly prepared by dilution from the clear, colorless content of ampules of a 1:1,000 solution of epinephrine, sterile physiologic solution of sodium chloride being added to make a dilution of 1:100,000 or 1:200,000. The solution was delivered by gravity from a graduated buret, the tip of which was connected with an 18 gage needle by means of rubber tubing. The rate of flow was accurately controlled by a fine needle valve inserted in the rubber tubing. The solution of epinephrine was administered in the antecubital vein of the left arm. Readings of the buret were made at thirty second intervals throughout the experiment, and the flow was maintained at the desired constant rate.

The measurements of blood pressure were made by the auscultatory method with a mercury manometer, with the standard cuff attached to the right arm. The heart rate was obtained either by means of continuous electrocardiographic tracings, using anteroposterior chest leads, or by use of a stethoscope strapped to the precordium, the number of beats in fifteen seconds being counted. For patients with cardiac irregularities the electrocardiographic method was used exclusively; for other patients the two methods were used interchangeably and gave essentially the same results. The basal metabolic rate and the consumption of oxygen were measured by means of a Benedict-Roth metabolism apparatus. From the curves obtained the respiratory rate, tidal air and respiratory minute volume were estimated. The basal metabolic rate was calculated according to the Aub-DuBois normal standards.⁷ Measurements of blood sugar were made by the method of Folin and Wu.⁸ The exercise tolerance of patients with angina pectoris was measured by the method of Riseman and Stern.⁹

The response to epinephrine was measured in seventeen subjects, eight men and nine women, whose ages varied from 18 to 64 years. Eighty-six studies of the effect of the intravenous injection of epinephrine were made.

Five patients, three with angina pectoris and two with rheumatic cardiac disease and congestive failure, were tested when the basal metabolic rate was normal and subsequently when various degrees of hypothyroidism developed following total ablation of the thyroid gland.

Two patients with myxedema were tested when the basal metabolic rate was approximately minus 30 per cent and also when the metabolism had been raised to normal by the oral administration of thyroid. One of these patients had spontaneous myxedema which developed several years following subtotal thyroidectomy performed for diffuse nodular goiter; the other patient had diabetes mellitus and myxedema induced by total ablation of the normal thyroid gland. The latter also had mitral stenosis, but at no time had she experienced signs or symptoms of cardiac failure nor had her activities been limited by the cardiac condition.

In addition to the aforementioned seven patients whose sensitivity to epinephrine was measured at different basal metabolic levels, ten other patients were

7. Aub, J. C., and DuBois, E. F.: Clinical Calorimetry: XIX. The Basal Metabolism of Old Men, *Arch. Int. Med.* **19**:823 (May) 1917.

8. Folin, O., and Wu, H.: A System of Blood Analysis: Supplement. A Simplified and Improved Method for the Determination of Sugar, *J. Biol. Chem.* **41**:367, 1920.

9. Riseman, J. E. F., and Stern, B.: A Standardized Exercise Tolerance Test for Use in Patients with Angina Pectoris on Exertion, *Am. J. M. Sc.* **188**:646, 1934.

RISEMAN ET AL.—CONGESTIVE HEART DISEASE

studied at a single metabolic level. The basal metabolic rate in these patients ranged between plus 12 and minus 34 per cent. Three of these patients had no cardiac abnormality, one had angina pectoris, one had paroxysmal auricular tachycardia and five had cardiac disease of the congestive type.

OBSERVATIONS

the patient rested

OBSERVATIONS

OBSERVATIONS

Effect of Epinephrine on the Blood Pressure.—After the patient rested in the recumbent position for one-half hour measurements of the blood pressure and the heart rate were made at thirty second intervals until constant levels were obtained. The needle was then inserted in the vein. After the blood pressure and heart rate had returned to the resting level, epinephrine was administered at the rate of 0.25 cc. (1:100,000 solution) per minute. The injection of epinephrine was continued at this rate until the blood pressure had maintained a stationary level for from two to five minutes. The rate of injection was then increased by increments of 0.25 cc. per minute, and the maximum effect of each new dose was determined in the same manner. The maximum response of the blood pressure to a given dose was usually obtained within two minutes after that rate of injection was started. The level of blood pressure remained relatively constant as long as the injection was continued at the same rate.

the dose necessary to maintain the systolic blood pressure 20 mm. of level was established, the injection was stopped and maintain the systolic blood pressure at the most

When the dose necessary to maintain the systolic blood pressure 20 mm. of mercury above the resting level was established, the injection was stopped. The amount of epinephrine necessary to increase and maintain the systolic blood pressure 20 mm. of mercury above the resting level proved to be the most satisfactory basis for estimating the effect of epinephrine on blood pressure. It was found early in the work that the administration of larger doses was unnecessary and was followed in some instances by a marked drop in the blood pressure after cessation of injection. In two patients, one with angina pectoris and one with paroxysmal auricular tachycardia, the systolic blood pressure was raised from an average of 190 mm. to approximately 270 mm. of mercury in an attempt to precipitate a typical attack. An attack was precipitated in the patient with angina pectoris; in both patients the systolic blood pressure following the cessation of injection of epinephrine fell to approximately 60 mm. of mercury, and the patients showed evidence of collapse from which they recovered several hours later. Untoward reactions following the subcutaneous or intramuscular injection of epinephrine have been observed by others.¹⁰ Administration by the intravenous route allows one to control the concentration of circulating epinephrine. The danger of exceeding the patient's tolerance can be obviated by starting with a small dose and observing the reaction of the patient to gradually increasing doses.

During the injection of doses of epinephrine which increased the systolic blood pressure by 20 mm. of mercury the patients showed definite pallor and experienced palpitation; attacks of angina pectoris were not produced by these doses. After cessation of injection the systolic blood pressure fell within three minutes to the previous resting level, and a pronounced flushing of the skin, especially marked in the face, became apparent. In three instance, because of subjective discomfort, the injection of epinephrine was stopped before a 20 mm. increase in systolic blood pressure was produced.

10. Cottrell, J. E., and Wood, F. C.: The Effect of Epinephrine in Angina Pectoris, *Am. J. M. Sc.* **181**:36, 1931. Katz, L. N.; Hamburger, W. W., and Lev, M.: The Diagnostic Value of Epinephrine in Angina Pectoris, *Am. Heart J.* **7**:371, 1932.

TABLE 1.—Sensitivity to Epinephrine in Patients Studied at Different Levels of Basal Metabolic Rate as Estimated by the Amount of Epinephrine * Required to Raise the Systolic Blood Pressure Approximately 20 Mm. of Mercury

Case	Diagnosis	Time of Study	Weight, Kg.	Basal Meta- bolic Rate, Percentage Deviation from Normal	Ephreph- rine Ce. per Minute of 1:100,000 Solution	Blood Pressure, Mm. of Mercury				Heart Rate, Beats per Minute		Comment
						Before Injection	During Injection	Total Ablation of Thyroid Gland	Before Injection	During Injection		
Patients Whose Basal Metabolic Rate Was Lowered by												
1	Angina pectoris	Before operation 4 days after operation 11 days after operation 16 days after operation 60 days after operation	57 55 55 57	-7 -12 -28 -29 -37	1.0 1.25 1.25 1.25 2.0	184/100 180/96 190/108 198/112 184/132	216/92 208/84 218/84 224/96 206/122	76 88 90 84 96	76 88 90 84 96	76 88 90 84 96	Anginal attacks at 57 to 96 trips Anginal attack at 105 trips No anginal attack at 200 trips No anginal attack at 200 trips; clinical myxedema	
2	Angina pectoris	Before operation 12 days after operation 21 days after operation	75 73 73	-10 -25 -27	0.85 0.85 1.50	200/100 180/90 216/112	226/118 206/86 242/110	66 64 68	66 64 68	66 64 68	Anginal attacks at 17 to 21 trips No angina clinically; trips not measured No angina clinically; trips not measured	
3	Angina pectoris	Before operation 3 days after operation 24 days after operation 45 days after operation 85 days after operation	59 59 59 59 62	-15 -11 -14 -29 -37	1.0 1.0 0.75 1.4 3.5	128/88 130/90 134/86 142/100 128/86	152/80 150/90 154/86 160/78 152/68	68 78 70 54 66	68 78 70 54 66	68 78 70 54 66	Anginal attacks at 32 to 36 trips No anginal attack at 72 trips 7 days after operation (nerve relief) Anginal attack at 36 trips (thyroid, 3 grains daily) No anginal attack at 200 trips No anginal attack at 200 trips; clinical myxedema	
4	Congestive heart failure (auricular fibrillation)	16 mos. after operation Before operation 5 days after operation 26 days after operation 38 days after operation	59 39 59 40 40	-32 +20 -6 -17 -27	3.25 0.5 0.5 0.5 0.5	128/96 118/90 114/90 116/90 116/94	150/84 132/90 128/86 126/84 126/90	64 78 86 88 78	64 78 86 88 78	64 78 86 88 78	Anginal attacks at 32 trips; clinical myxedema Injection stopped because of subjective discomfort Injection stopped because of subjective discomfort Injection stopped because of subjective discomfort Mild clinical myxedema; thyroid not necessary	
5	Congestive heart failure	Before operation 5 days after operation 32 days after operation 109 days after operation	61 55 65 70	-11 -11 -31 -33	1.25 1.0 1.25 1.25	114/68 114/68 114/74 102/70	134/64 138/62 144/66 120/66	58 64 66 56	58 64 66 56	58 64 66 56	Mild clinical myxedema; thyroid not necessary Mild clinical myxedema; thyroid not necessary	
Patients Whose Basal Metabolic Rate Was Increased by Thyroid Medication												
6	Spontaneous myxedema	Before medication Thyroid, 2 grains daily	54 50	-30 ± 0	6.0 1.75	100/76 110/74	120/86 130/82	74 94	74 94	74 94	Marked clinical myxedema No myxedema	
7	Diabetes mellitus, total ablation of thyroid	Before medication Thyroid, 1/4 grain daily Thyroid, 5 grains daily 8 days after thyroid was omitted	58 58 50 50	-34 -25 + 8 - 5	1.5 1.5 0.75 0.75	116/84 110/90 110/68 104/70	140/90 134/92 136/68 126/68	90 88 120 88	90 88 120 88	90 88 120 88	Marked clinical myxedema No myxedema	

* Cubic centimeters per minute of 1:100,000 solution injected intravenously.

† Before operation in this patient some of the exercise tolerance tests were made during attacks of gout. At such times his exercise tolerance was diminished to approximately 60 trips, whereas when free from attacks of gout his tolerance was approximately 90 trips.

‡ The thyroid used throughout this work satisfied the requirements outlined in the "Pharmacopoeia of the United States," which were recently discussed in an article in The Journal of the American Medical Association (Means, J. H.: Therapeutics of the Thyroid, J. A. M. A. 105: 24 [July 6] 1935).

Systolic Blood Pressure: There was no relationship between the response of the systolic blood pressure to epinephrine and the type of cardiovascular disease or the level of the blood pressure while at rest (table 1). A progressive increase in the rate of flow of the solution of epinephrine was followed by a progressive increase in the systolic blood pressure. The dose of epinephrine necessary to cause a rise of approximately 20 mm. in the systolic blood pressure in a given subject on different days under the same conditions varied by no more than 0.25 cc. (1:100,000 solution) per minute. The sensitivity of different persons,

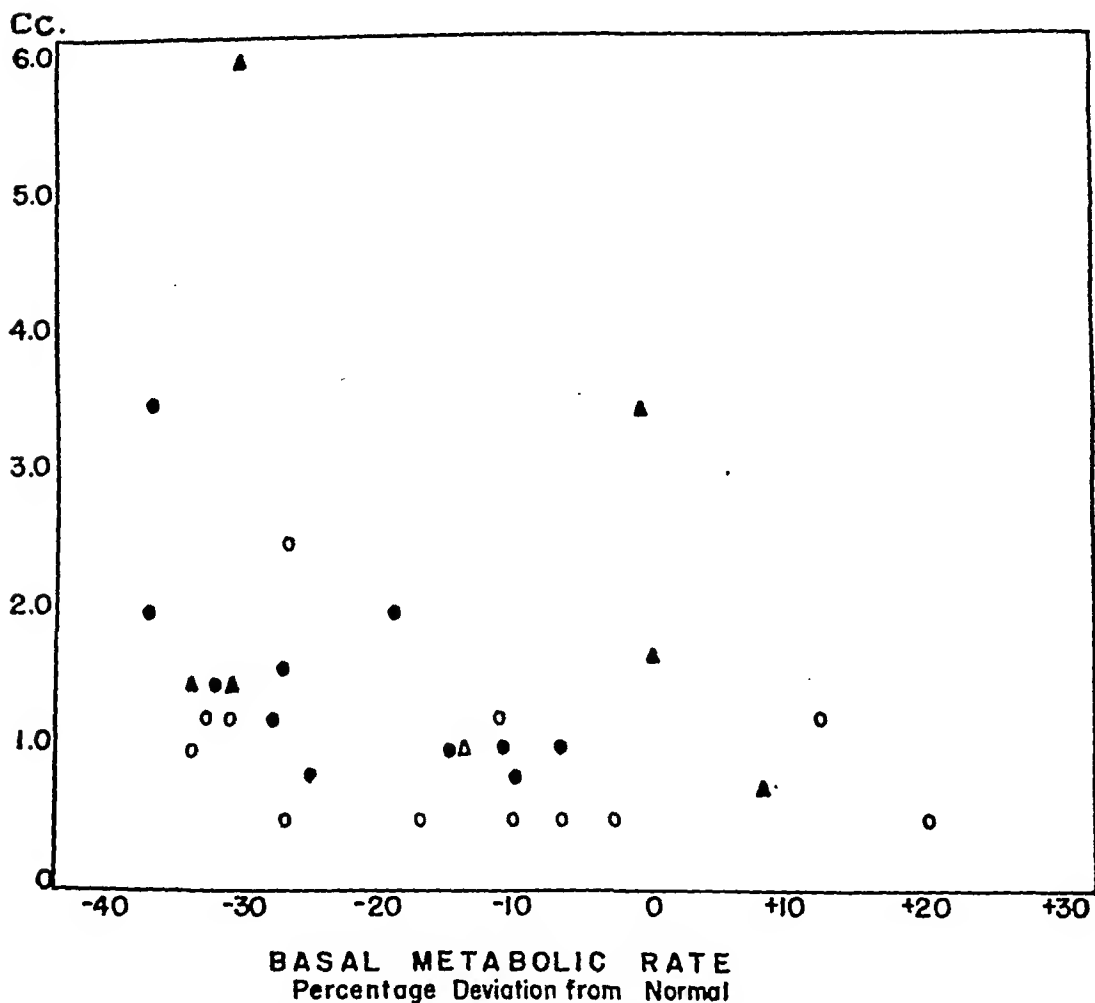


Chart 1.—The dose of epinephrine in cubic centimeters per minute of 1:100,000 solution required to raise the systolic blood pressure 20 mm. of mercury. The subjects studied included patients with various types of chronic cardiac disease (angina pectoris, indicated by the solid circle; congestive failure, indicated by the open circle, and paroxysmal auricular tachycardia, indicated by the open triangle) and subjects with no cardiac disease (indicated by the solid triangle).

however, varied considerably, whether expressed in terms of cubic centimeters of 1:100,000 solution per minute or in milligrams per kilogram per minute. The dose of epinephrine (1:100,000 solution) necessary to raise the systolic blood pressure 20 mm. of mercury varied from 0.5 cc. (0.00013 mg. per kilogram per minute) to 6 cc. (0.0011 mg. per kilogram per minute) in the different patients studied (table 1 and chart 1).

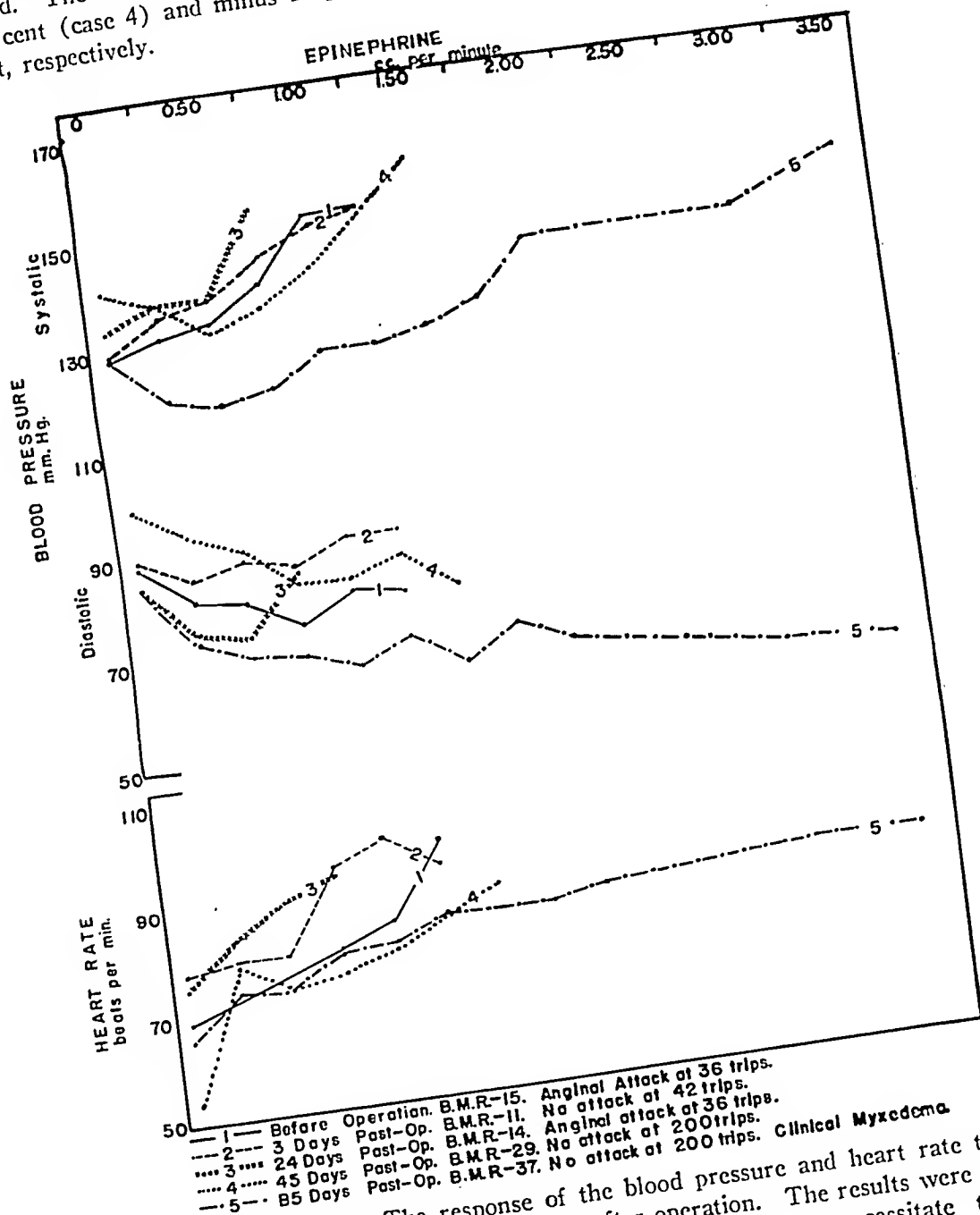
No definite correlation was evident between the response of the systolic blood pressure to epinephrine and basal metabolic rates between normal and minus 30 per cent; when, however, the basal metabolic rate was below minus 30 per cent and clinical evidences of severe myxedema were present some patients were definitely less sensitive to epinephrine (chart 1). In twenty-six of the thirty tests, regardless of the basal metabolic rate, from 0.5 to 2 cc. was required to raise the systolic blood pressure approximately 20 mm. of mercury. Of the four patients in whom more than 2 cc. was necessary three had basal metabolic rates between minus 29 and minus 37 per cent and showed clinical evidences of marked myxedema. It should be noted, however, that other patients with equally striking signs of myxedema and similarly reduced metabolic rates required only the usual dose of epinephrine.

In order to study more accurately possible changes in the response of the blood pressure to epinephrine at various metabolic levels, tests were repeatedly performed in seven patients when their basal metabolic rates were changed either by total thyroidectomy or by thyroid medication (table 1).

Three patients with angina pectoris were studied before and after total ablation of the thyroid gland. One of these patients (case 1, table 1) required 1 cc. of a 1:100,000 solution of epinephrine per minute to cause a rise in the systolic blood pressure of 32 mm. of mercury before operation when the basal metabolic rate was minus 7 per cent. Four days after the operation, when the metabolic rate had fallen to minus 12 per cent, there was no significant difference in the dosage necessary to cause a similar response in blood pressure, the variation from 1 to 1.25 cc. being within the limits of error of the method. Eleven and sixteen days after the operation, when the basal metabolic rates were minus 28 and minus 29 per cent, respectively, 1.25 cc. of epinephrine again caused the same response. A decrease in the basal metabolic rate from minus 7 to minus 29 per cent was thus accompanied by no appreciable change in the sensitivity to epinephrine. Sixty days later, when the basal metabolic rate became minus 37 per cent, the patient showed signs and symptoms of myxedema sufficient to make thyroid medication advisable. For the first time the patient was definitely less sensitive to epinephrine, 2 cc. being required to cause a rise in the systolic blood pressure of 22 mm. of mercury.

In another patient with angina pectoris (case 3, table 1) the basal metabolic rate was minus 15 per cent before the operation, and 1 cc. of epinephrine per minute caused a rise in the systolic blood pressure of 24 mm. of mercury. Three days after the operation the basal metabolic rate was minus 11 per cent and the response of the blood pressure to epinephrine was unchanged (table 1 and chart 2). For reasons stated later the basal metabolism of this patient was maintained during the next three weeks at the preoperative level by thyroid medication. The response to epinephrine was essentially unchanged (table 1). Thyroid medication was then discontinued; forty-five days after the operation the basal metabolic rate was minus 29 per cent and 1.4 cc. of epinephrine per minute induced a rise in the systolic pressure of 18 mm. of mercury. When the basal metabolic rate had become minus 37 per cent (eighty-five days after operation) signs and symptoms of myxedema severe enough to require thyroid medication were evident. A definite decrease in the sensitivity to epinephrine was evidenced for the first time, 3.5 cc. of epinephrine being required to induce a rise of 24 mm. of mercury in the systolic blood pressure (table 2 and chart 2). The results in the third patient with angina pectoris were in accord with these observations (table 1).

The two patients with congestive cardiac disease (cases 4 and 5, table 1) showed no change in response of the blood pressure to epinephrine at any time up to one month and three and a half months after total ablation of the thyroid gland. The basal metabolic rate in these two patients decreased from plus 20 per cent (case 4) and minus 11 per cent (case 5) to minus 27 and minus 33 per cent, respectively.



One patient with spontaneous myxedema (case 6, table 1) and marked symptoms required as much as 6 cc. of epinephrine to cause an increase of 20 mm. in the systolic blood pressure. When the basal metabolic rate was raised to normal 1.75 cc. caused the same response of the blood pressure. Another patient.

TABLE 2.—Oxygen Consumption and Respiratory Studies During Intravenous Administration of Epinephrine to Patients with Levels of Basal Metabolic Rate Varying from Plus 14 to Minus 35

Case*	Diagnosis	Time of Study	Level of Basal Epinephrine,† Percentage Deviation from Normal	Blood Pressure, Mm. of Mercury		Oxygen Consumption		Respiratory Rate, Respirations per Minute		Respiratory Minute Volume, Liters per Minute	
				Before Injection	During Injection	Before Injection, Cc. per Minute	During Injection, Percentage Increase	Before Injection	During Injection	Before Injection	During Injection
2	Angina pectoris	Before total thyroidectomy	-7	183/98	226/90	180	24	13	19	4.5	7.0
				190	12	15	18	4.5	6.0
		From 19 to 22 days after total thyroidectomy	-27	216/112	220/110	165	17	13	15	3.8	5.6
			1.5	216/112	242/110	160	34	15	20	5.0	6.2
3	Angina pectoris	Before total thyroidectomy	-15	128/88	152/80	165	22	16	21	5.5	10.0
			0.5	128/88	134/80	165	15	15	20	5.5	10.0
		From 46 to 49 days after total thyroidectomy	-29	142/100	160/78	145	17	15	18	5.5	10.0
			1.0	142/100	142/82	155	19	13	17	4.5	8.0
			0.5	142/100	132/90	140	21	16	18	6.0	9.5
6	Spontaneous myxedema	Before medication	-30‡	100/76	120/86	135	22	17	24	5.5	8.0
			2.0	100/76	98/76	130	22	15	19	4.5	5.5
		Thyroid, 2 grains daily	± 0	110/74	130/82	180	28	24	33	8.0	13.0
			1.0	110/74	128/84	170	16	25	38	10.5	16.0
			0.5	110/74	126/90	180	19	28	35	10.0	13.0
8	Congestive heart failure	Before total thyroidectomy	+14	240/120	282/102	180	20	20	24	5.5	7.5
			1.0	240/120	260/100	175	26	23	30	7.0	9.5
			0.5	240/120	256/100	185	27	20	25	6.0	9.0
9	Congestive heart failure	Before total thyroidectomy	± 0	190/118	216/100	165	27	18	23	6.0	7.0
			0.25	170	13	20	26	6.0	7.5
10	Congestive heart failure	Before total thyroidectomy	-12	112/72	130/58	180	15	16	19	5.0	7.0
			0.25	112/72	118/56	165	18	15	20	4.5	7.5
11	Congestive heart failure	Three months after total thyroidectomy	-35‡	102/86	150/80	145	16	8	11	3.5	5.0
			1.0	102/86	130/70	150	15	8	11	3.5	5.5
			0.5	102/86	114/76	160	11	6	8	3.5	4.5

* Cases 2, 3 and 6 of this table are those of the same number in table 1.

† The level of basal metabolism represents the average of many measurements of the basal metabolic rate made on days just preceding the tests with epinephrine.

‡ Clinical evidences of marked myxedema were present.

with diabetes mellitus and myxedema induced by total ablation of the thyroid gland (case 7, table 1) required 1.5 cc. of epinephrine when the basal metabolic rate was minus 34 and minus 25 per cent, and 0.75 cc. when the metabolic rate was brought to normal and the symptoms of myxedema relieved. In these two patients no tests were made when the basal metabolism was at intermediate levels.

The results in the patients studied show little or no change in the response of the systolic blood pressure to epinephrine as the basal metabolic rate varied from normal to approximately minus 30 per cent. When, however, signs and symptoms of severe myxedema developed with a basal metabolic rate of minus 30 per cent or lower some patients were less sensitive to epinephrine which was injected. This was evident in five patients, in two of whom (cases 3 and 6, table 1) the decrease in sensitivity was striking; in three others (cases 1, 2 and 7, table 1) the decreased sensitivity was relatively slight, being apparent only by comparison with the results obtained when symptoms of myxedema were not present. Although the response of the blood pressure was considerably decreased in cases 3 and 6 when the patients showed evidences of clinical myxedema, it is interesting to note that other patients with normal metabolic rates required a similar dose to evoke the same response (chart 1).

Diastolic Blood Pressure: With the doses of epinephrine which caused a rise in the systolic blood pressure of 20 mm. of mercury, the diastolic blood pressure usually showed either a slight decrease or no change (tables 1 and 2).¹¹ The response of the diastolic blood pressure during the injections of epinephrine was not related to the underlying cardiovascular condition, the resting blood pressure, the basal metabolic rate or the degree of clinical myxedema.

Effect of Epinephrine on the Heart Rate.—When the systolic blood pressure was increased 20 mm. of mercury the heart rate usually increased between 6 and 22 beats per minute (table 1). In approximately one-half the experiments the change in heart rate was less than 10 beats per minute. Whereas the systolic blood pressure increased progressively as the dose of epinephrine was increased, no constant relationship was observed between changes in the heart rate and the magnitude of dosage (tables 1 and 2).

Changes in heart rate were not related to the resting heart rate or to the state of the cardiovascular system. Patients with angina pectoris, congestive cardiac disease or paroxysmal auricular tachycardia, regardless of the underlying etiology, all responded in a similar manner. In one of five patients with auricular fibrillation, however, the heart rate increased 100 beats per minute with the dose of epinephrine which caused a rise in systolic blood pressure of 18 mm. of mercury. This unusual response may have been related to insufficient digitalization.

The heart rate at rest was essentially unchanged in the five patients after total thyroidectomy when the metabolic rate was lowered and clinical improvement was manifest (table 1). In the two patients with marked clinical myxedema who were studied during treatment with thyroid (cases 6 and 7, table 1) the basal heart rate was increased when the basal metabolic rate was raised to normal, and the rise in the ventricular rate during the injection of epinephrine was somewhat greater. Despite the normal basal metabolic rate in these two patients after thyroid medication they showed elevated basal pulse rates, flushing, excessive perspiration

11. In addition to the changes in blood pressure and heart rate which appear in tables 1 and 2, data on six other patients have been collected and show essentially the same findings.

and hyperactivity similar to that seen in patients with mild hyperthyroidism. This tendency of patients with myxedema to show evidence of mild hyperthyroidism after thyroid medication has been noted by others.¹²

No relationship between the basal metabolic rate and the response of the heart rate to epinephrine was evidenced in eighty-five tests made on seventeen subjects with basal metabolic levels from minus 37 to plus 20 per cent. In four patients changes in response of the heart rate were apparent when results in the same subjects were compared at different levels of basal metabolism (table 1). In cases 1 and 5 (table 1) when the basal metabolic rates were lowered to minus 33 and minus 37 per cent, respectively, the heart rate for the first time failed to respond appreciably to the injection of epinephrine, although the characteristic rise in blood pressure was elicited. In cases 6 and 7 (table 1) when the metabolism was raised to normal by thyroid, injection of epinephrine caused a greater increase in the heart rate.

Consumption of Oxygen and Respiration During Injection of Epinephrine.—The consumption of oxygen, the respiratory rate, the tidal air and the respiratory minute volume were studied in seven patients whose basal metabolic rate levels ranged from plus 14 to minus 35 per cent. Two patients who had angina pectoris were studied before and after total ablation of the thyroid gland; one patient with spontaneous myxedema was studied before and after thyroid therapy (table 2). All tests were performed with the patient in the postabsorptive state. The subjects had been accustomed to the Benedict-Roth metabolism apparatus. Control curves were obtained under basal conditions and also with the needle inserted in the vein. The results of these two measurements of the metabolic rate agreed satisfactorily with each other and with the basal metabolic rate measured on other days. During the course of recording the control curve, with the needle in place, the epinephrine was injected intravenously at the rate which had been found previously to cause an increment in systolic blood pressure of 20 mm. of mercury. On a subsequent date the test was repeated with a different dose of epinephrine. Measurements of blood pressure and pulse rate were made before and during the injection; the results were in accord with those found on other occasions when observations on the respiration and the consumption of oxygen had not been made.

The consumption of oxygen reached a maximum between one and two minutes after the injection of epinephrine at a given rate was begun and remained fixed at that level throughout the test. The doses of epinephrine utilized (from 0.25 cc. to 6 cc. per minute, table 2) caused increments from 11 to 34 per cent over the basal consumption of oxygen. The degree of increase showed no constant relationship to the dose of epinephrine, to the response of the systolic blood pressure or to the basal metabolic rate.

The intravenous administration of epinephrine invariably caused an appreciable increase in the respiratory rate and in the respiratory minute volume. The depth of respiration did not always increase. No relationship was apparent between the respiratory changes and the dose of epinephrine or the basal metabolism. The respiratory response of patients with congestive failure was not different from that of the other patients studied.

Response of the Blood Sugar.—The concentration of dextrose in the venous blood was measured immediately before the injection of epinephrine was begun and two

12. (a) Morris, R. M.; Witter, M. S., and Weiss, S.: An Unusual Sensitizing Action of Thyroid Substance on the Effect of Epinephrine in Man, *Proc. Soc. Exper. Biol. & Med.* **21**:149, 1923. (b) Means, J. H., and Richardson, E. P.: *The Diagnosis and Treatment of Diseases of the Thyroid*, Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 4, p. 299.

minutes after the injection was stopped. A rise in the blood sugar content occurred during the administration of epinephrine, the average rise being about 10 mg. per hundred cubic centimeters. The extent of the rise of the blood sugar content was not related to the level of the basal metabolic rate or to the dose of epinephrine administered. In the patient with diabetes the blood sugar content did not show this characteristic increase, probably owing to the effect of insulin which had been administered several hours previously.

RELATIONSHIP BETWEEN SENSITIVITY TO EPINEPHRINE AND
CLINICAL IMPROVEMENT AFTER TOTAL THYROIDECTOMY
IN PATIENTS WITH CARDIAC DISEASE

In two patients with angina pectoris and in two patients with congestive failure an exceptional opportunity was afforded to study the relationship between clinical improvement and sensitivity to epinephrine. The findings in each subject at various times after operation were compared with those observed in the same subject before operation. In the two patients with angina pectoris the degree of clinical improvement was evaluated by the clinical course and by a standardized exercise tolerance test.⁹

In case 3 (table 1 and chart 2) the basal metabolism before operation was minus 15 per cent, and 1 cc. of a 1:100,000 solution of epinephrine per minute caused a rise in the systolic blood pressure of 24 mm. of mercury. Preoperatively daily attacks of angina occurred on exercise or on emotion and also while the patient was at rest in bed. Thirty-two trips under standardized conditions on the two step staircase regularly precipitated a characteristic attack of angina. During the first week after operation the patient was free from anginal attacks while at rest in bed, and 72 trips on the staircase failed to produce an anginal attack. However, the basal metabolic rate and the sensitivity to epinephrine remained essentially unchanged. This relief from pain immediately after operation, which is unrelated to changes in the metabolic rate or in sensitivity to epinephrine, has been extensively studied and has been shown to be due to interruption of sensory nerve impulses from the heart to the central nervous system at the time of operation.¹³ To obviate the complicating effect of this early "nerve relief" in our studies of the relationship of changes in sensitivity to epinephrine to clinical improvement in this patient thyroid was administered in sufficient dosage to maintain the metabolic rate at the preoperative level until the temporary effect of interruption of nerve impulses had disappeared. Beginning with the seventeenth day after operation attacks of pain were again precipitated on exertion. At first, 55 trips were required, but the amount of exercise necessary to produce angina gradually decreased until on the twenty-fourth postoperative day typical anginal attacks were precipitated by the same amount of work that had induced attacks before operation. The administration of thyroid had maintained the basal metabolic rate at the preoperative level, and the sensitivity to epinephrine was still unchanged.

13. Weinstein, A. A.; Davis, D.; Berlin, D. D., and Blumgart, H. L.: The Mechanism of the Early Relief of Pain in Patients with Angina Pectoris and Congestive Failure After Total Ablation of the Normal Thyroid Gland, *Am. J. M. Sc.* **187**:753, 1934.

After the factor of relief of pain due to the effect of interruption of nerve impulses was no longer operative in this patient the relationship between various degrees of hypothyroidism and the sensitivity to epinephrine could be studied uncomplicated by other factors. Thyroid medication was then omitted. Forty-five days after operation the basal metabolic rate decreased to minus 29 per cent, and anginal attacks were not experienced spontaneously or after 200 trips on the staircase. A rise in systolic blood pressure of 18 mm. of mercury was produced by 1.4 cc. of epinephrine. Six weeks after this improvement was manifest, however, the basal metabolic rate had become minus 37 per cent and signs and symptoms of severe myxedema were evident. At this time the sensitivity to epinephrine was definitely decreased, 3.5 cc. being required to cause a rise of systolic blood pressure of 24 mm. of mercury (table 1 and chart 2).

Similar results were observed in case 1 by studies before and after operation (table 1). Preoperatively attacks of angina were produced after from 57 to 96 trips on the staircase. There was no evidence that the factor of early relief by the interruption of nerve impulses was of importance in this patient, for an attack of angina had been induced by 105 trips on the eleventh postoperative day. Sixteen days after total thyroidectomy when the basal metabolic rate had decreased to minus 29 per cent the patient for the first time was able to perform 200 trips without an anginal attack. The sensitivity to epinephrine was essentially the same as before the operation and at the time of two earlier postoperative tests made four days and eleven days after operation. Clinical improvement was maintained uninterruptedly. Nine weeks after the operation a slight decrease in sensitivity to epinephrine became evident. Clinical myxedema had developed, and the basal metabolic rate was minus 37 per cent.

In these two patients who were observed in the hospital the effect of early relief "nerve"¹³ could be excluded, and the relationship of clinical improvement to altered sensitivity to epinephrine and to the degree of hypothyroidism could be studied with exceptional accuracy. Conspicuous clinical improvement was reflected by quantitative exercise tolerance tests and the clinical course at a time when no significant changes in the sensitivity to epinephrine could be detected. With the development of clinical myxedema the patients became relatively less sensitive to epinephrine; the clinical course was not favorably affected.

The two patients with congestive cardiac failure (cases 4 and 5, table 1) showed no change in sensitivity to epinephrine at any time up to one and three and one-half months after operation. Beginning one month after operation it was possible for them to undertake considerably more activity without precipitating any evidence of congestive failure than was possible before the operation. The absence of decreased sensitivity to epinephrine at the time when clinical improvement became manifest in these patients is in accord with our observations in the patients with angina pectoris.

These observations showed that relief from angina pectoris and congestive cardiac failure develops and persists at metabolic levels at which no significant changes can be detected in the sensitivity of the cardiovascular system to continuous intravenous injection of epinephrine. Such persistent improvement is rather to be related to the lessened work of the heart when hypothyroidism, as evidenced by a lowered basal metabolic rate, is induced.

COMMENT

Measurement of the sensitivity of patients to epinephrine before and after total ablation of the normal thyroid gland affords a direct approach to the study of the significance of changes in sensitivity to epinephrine in the improvement caused by this procedure.

In most investigations in which epinephrine has been administered the drug has been given subcutaneously or intramuscularly. When so given the drug acts first on the local blood vessels, and the rate of absorption is consequently irregular and beyond control. At times the response is delayed and prolonged,³ at other times a dangerous reaction and even coronary thrombosis may occur¹⁰ because of unduly rapid absorption. The nature of the response varies in different persons and even may vary considerably from day to day in the same person. The intravenous injection of epinephrine under the controlled conditions outlined previously is relatively safe and offers many advantages. The amount introduced is immediately physiologically active and can be accurately controlled. If any untoward symptoms or signs develop injection can be interrupted and the effects soon terminated. Administration of the same solution to the same persons on different days produces extraordinarily uniform responses, and so the effect of variation in but one physiologic factor such as the metabolic level can be accurately studied.

The results presented earlier indicate that the intravenous administration of epinephrine to human subjects is followed by a definite and characteristic increase in the systolic blood pressure, heart rate, oxygen consumption of the body, rate and depth of respiration and blood sugar content. The response of the blood pressure signifies the effect of epinephrine on the vasomotor system; the changes in ventricular rate indicate the effect of epinephrine on the sinus node, and changes in the consumption of oxygen, the effect of epinephrine on the tissues of the body in general. In addition to the factors studied in this investigation other effects of epinephrine are recognized, such as the ability to produce extra ventricular systoles.¹⁴ The changes which we have reported in this paper, however, are those which are generally accepted as indexes of epinephrine activity and are those which are closely linked with the physiologic activity of the cardiovascular system in man. The effect of epinephrine on the cardiac minute volume output of man will be the subject of a forthcoming communication.

14. Nahum, L. H., and Hoff, H. E.: The Mechanism of Sudden Death in Experimental Acute Benzol Poisoning, *J. Pharmacol. & Exper. Therap.* **50**:336, 1934. Nathanson, M.: A Method for the Study of the Rhythmic Property of the Human Heart, *Proc. Soc. Exper. Biol. & Med.* **30**:967, 1933.

The systolic blood pressure was found to be the most delicate index of the patient's sensitivity to epinephrine and was the only measurement which showed a progressive rise as the dose of epinephrine was increased. The rise of the systolic blood pressure in our subjects with and without cardiovascular disease was similar to that observed by Weinberg⁵ and Cori and Buckwald,^{2c} who also gave the drug by continuous intravenous drip to normal human subjects. The amount of epinephrine necessary to influence the blood pressure apparently varies in different persons. We have found no evidence, however, that patients with angina pectoris or valvular cardiac disease are more sensitive than normal persons. Petersen and Levinson¹⁵ found that patients with a cardiovascular renal condition reacted to epinephrine in a manner similar to that of normal persons.

The heart rate of human beings with a normal basal metabolic rate is only slightly increased by the action of epinephrine. This is shown by the work of Goetsch,¹⁶ Peabody, Sturgis, Tompkins and Wearn,¹⁷ Sandiford,¹⁸ Rogers,¹⁹ Hinton,²⁰ Blumgart²¹ and Cori and Buckwald^{2c} as well as by the observations recorded in this communication. These findings are contrary to the results obtained with the use of the denervated cat's heart. As Cannon²² has shown, the "denervated cat's heart is exquisitely sensitive to variations in the adrenin content of the circulating blood." This is brought about by two factors: 1. Following interruption of sympathetic nerve pathways the response of epinephrine becomes abnormally enhanced.²³ 2. In preparing the denervated heart

15. Petersen, W. F., and Levinson, S. A.: The Skin Reactions, Blood Chemistry and Physical Status of "Normal" Men and of Clinical Patients, *Arch. Path.* **9**:243 (Jan., pt. 2) 1930.

16. Goetsch, E.: Studies on Disorders of the Thyroid Gland. Hypersensitivity Test with Especial Reference to "Diffuse Adenomatosis" of the Thyroid Gland, *Endocrinology* **4**:389, 1920.

17. Peabody, F. W.; Sturgis, C. C.; Tompkins, B. M., and Wearn, J. T.: Epinephrine Hypersensitivity and Its Relation to Hyperthyroidism, *Am. J. M. Sc.* **161**:508, 1921.

18. Sandiford, I.: The Effect of the Subcutaneous Injection of Adrenalin Chloride on the Heat Production, Blood Pressure and Pulse Rate in Man, *Am. J. Physiol.* **51**:407, 1920.

19. Rogers, L.: The Adrenalin Test for Thyrotoxicosis, *Lancet* **2**:970, 1928.

20. Hinton, J. W.: The Adrenalin Test and Cholesterol Determinations in the Diagnosis of Borderline Hyperthyroidism, *Am. J. M. Sc.* **180**:681, 1930.

21. Blumgart, H. L.: The Circulatory Response to Epinephrine, *Libman Anniv. Vol.* **1**:215, 1932.

22. Cannon, W. B.: Studies on the Conditions of Activity in Endocrine Organs: XXVII. Evidence that Medulliadrenal Secretion is Not Continuous, *Am. J. Physiol.* **98**:450, 1931.

23. Meltzer, S. J., and Auer, C. M.: Studies on the "Paradoxical" Pupil Dilation by Adrenalin, *Am. J. Physiol.* **11**:218, 1904. Elliott, T. R.: The Action of Adrenalin, *J. Physiol.* **32**:439, 1905. Freeman, N. E.; Smithwick, R. H., and White, J. C.: Adrenal Secretion in Man, *Am. J. Physiol.* **107**:529, 1934.

care is taken to sever all the nerve pathways which normally inhibit the action of epinephrine. The operative procedure, therefore, makes the denervated heart preparation an extremely delicate indicator of the presence of circulating epinephrine. This preparation, however, does not give insight into the action of epinephrine on the normal intact cardiovascular system.

The consumption of oxygen by man is increased by injections of epinephrine, as shown by our observations and those of Sandiford,¹⁸ Castex and Schteingart,²⁴ Blumgart²¹ and Cori and Buckwald.^{2c} In our experience with graded dosages of epinephrine no close relationship between the dosage and the increment in the oxygen consumption was found. The maximum increase which we observed was 34 per cent. This observation is in general accord with the findings of others who gave the drug subcutaneously, intramuscularly or intravenously.²⁵ Our observations (table 2) and those of Castex and Schteingart²⁴ have shown that the increase in consumption of oxygen caused by epinephrine is the same in persons with hypothyroidism as in persons whose basal metabolic rate is normal. The observations of Sandiford¹⁸ are in general accord with these findings, although two of her patients with basal metabolic rates of minus 30 and minus 40 per cent showed a somewhat lessened response.

The results obtained in this investigation are somewhat different than might be expected from a survey of the literature on the interrelation of the thyroid and the adrenal glands and the effect of these glands on the cardiovascular system. The chief difficulties which attend the application of previous knowledge to the interrelationship of these glands in man and their influence on clinical cardiovascular conditions arise from the following factors: (1) the variation in reaction of different species to epinephrine; (2) the hazards of applying observations made on animals to cardiac conditions which occur only in man; (3) the necessity of extirpating all thyroid tissue to insure the development of hypothyroidism, and (4) the technical difficulties attending the removal of all thyroid tissue.

The marked differences in the response of different species to epinephrine² and the inadvisability of applying the results noted in experimental animals to the interpretation of disordered cardiovascular states in intact human beings have been commented on earlier in this communication. Although removal of the thyroid gland might be

24. Castex, M. R., and Schteingart, M.: Action de l'adrenaline sur la dépense calorique, la calcémie et la potassémie chez l'homme normal au atteint de troubles thyroïdiens, *Compt. rend. Soc. de biol.* **99**:1649, 1928.

25. Sandiford.¹⁸ Castex and Schteingart.²⁴ Blumgart.²¹ Cori and Buckwald.^{2c}

expected to lead to hypothyroidism, evidence exists that even an extraordinarily small amount of thyroid tissue which may not be removed frequently undergoes hypertrophy and maintains a normal metabolic rate both in animals and in man. Halsted²⁶ found that complete removal of all thyroid tissue followed by reimplantation of a minute bit of thyroid into the rectus abdominis muscle was followed by hypertrophy of the transplanted fragment and the absence of signs of hypothyroidism. The earlier failures of one of us (H. L. B.)²⁷ and those of others²⁸ to induce persistent hypothyroidism by maximal subtotal removal of the thyroid gland demonstrate the necessity of removing every vestige of the normal thyroid tissue. The necessity of total ablation of the thyroid to insure the permanently lowered metabolic rate of hypothyroidism is in contrast to the effectiveness of subtotal removal of the abnormal gland in lowering the metabolic rate of thyrotoxicosis to normal. The frequent occurrence of aberrant thyroid tissue in animals²⁹ is often the cause of the absence of hypothyroidism even after the entire gland itself is removed. The absence of measurements of the metabolic rate in some investigations makes it impossible to learn the degree to which this factor operates.

After complete extirpation of the thyroid in man, hypothyroidism develops gradually, the basal metabolic rate becoming appreciably lowered; not earlier than the end of the first week, and frequently not before the sixth to the eighth week, are markedly low levels reached. In animals some experiments have been performed immediately or within a few hours after thyroidectomy when the metabolic rate was presumably not lowered and before hypothyroidism could have developed.

The clinical improvement which follows total ablation of the thyroid gland is independent of changes in the sensitivity of epinephrine. Results of the present investigation demonstrate that the sensitivity of the cardiovascular system to epinephrine in our patients as reflected

26. Halsted, W. S.: Report of a Dog Maintained in Good Health by a Parathyroid Autograft Approximately One-Fourth of a Millimeter in Diameter, and Comments on the Development of the Operation for Graves' Disease as Influenced by the Results of Experiments on Animals, *J. Exper. Med.* **15**:205, 1912.

27. Friedman, H. F., and Blumgart, H. L.: Treatment of Chronic Heart Disease by Lowering the Metabolic Rate: IV. The Necessity for Total Ablation of the Thyroid, *J. A. M. A.* **102**:17 (Jan. 6) 1934.

28. Rose, E.: Malignant Hypertensive Vascular Disease Simulating Hyperthyroidism: Clinical Course Following Maximal Subtotal Thyroidectomy, *M. Clin. North America* **16**:261, 1932. Deutrebände, L.: Personal communication to the authors.

29. Marine, D., and Lenhart, C. H.: The Influence of Glands with Internal Secretions on the Respiratory Exchange: I. Effect of Subcutaneous Injection of Adrenalin on Normal and Thyroidectomized Rabbits, *Am. J. Physiol.* **54**:248, 1920.

by the response of the blood pressure and ventricular rate is the same before operation, within a few days after operation and later in the postoperative course when, according to our practice, a moderate degree of hypothyroidism is maintained. These results are not in complete accord with those of Eppinger and Levine,³⁰ who injected epinephrine intramuscularly and found either the same response or a somewhat lessened response of the blood pressure and pulse rate a few days after operation. If a decreased sensitivity to epinephrine were an important factor in conferring relief on patients after total thyroidectomy a relationship between these two phenomena should be apparent. Clinical improvement in our patients was evident, however, long before any demonstrable change in sensitivity to epinephrine occurred, and many patients showed persistent clinical improvement without showing decreased sensitivity to epinephrine. Observations which have been presented in an earlier communication¹³ demonstrate that the absence of pain which has been observed soon after operation under conditions of rest³¹ or exercise (case 3)¹³ or after injections of epinephrine³⁰ is due to the interruption of sensory impulses from the heart to the central nervous system. After the effect of the early interruption of nerve pathways is no longer apparent clinical relief persists without any change in sensitivity to epinephrine (cases 1 and 3).

No significant change in the response to epinephrine was observed in our cases when the basal metabolic level varied from the normal to approximately minus 30 per cent. When the basal metabolism was lower than minus 30 per cent and signs and symptoms of clinical myxedema became manifest the response of the blood pressure and heart rate was in some instances lessened and in other instances unchanged. These findings are in accord with the observations of Sandiford.¹⁸ In addition, Sandiford found a somewhat decreased increment in the oxygen consumption after the subcutaneous injection of epinephrine in two patients with spontaneous myxedema and basal metabolic rates of minus 30 and minus 40 per cent.

Several patients with angina pectoris who failed to obtain complete relief from pain when the basal metabolism was maintained at a level of approximately minus 30 per cent showed additional relief when the basal metabolism was allowed to decrease to lower levels at which some of the distressing symptoms of myxedema were experienced. Although a decreased sensitivity to epinephrine is not evident in all patients with the metabolic rates at such levels, this factor may contribute to the

30. Eppinger, E. C., and Levine, S. A.: Effect of Total Thyroidectomy on Response to Adrenalin, *Proc. Soc. Exper. Biol. & Med.* **31**:485, 1934.

31. Blumgart, Riseman, Davis and Berlin.¹ Weinstein, Davis, Berlin and Blumgart.¹³

additional improvement witnessed in some patients with metabolic levels below minus 30 per cent.

One might consider that although the sensitivity of the cardiovascular system is unchanged the amounts of epinephrine produced by the adrenal glands after total thyroidectomy conceivably might be reduced and the heart subjected to less intense stimuli. Unfortunately, quantitative tests for measuring the concentration of circulating epinephrine in man are not available. Certain facts, however, make it appear most unlikely that a diminished production of epinephrine post-operatively, either at rest or on exertion, plays a significant rôle in the improvement observed in our patients. If after operation a lessened amount of epinephrine were produced at rest one would expect the heart rate and blood pressure during rest to be definitely decreased, and larger amounts of epinephrine injected intravenously should be required to cause the systolic blood pressure and the heart rate to reach the same heights as before operation. This has not been our experience. Similarly, there is no evidence that the production of epinephrine on exercise is diminished after operation. If a lesser secretion of epinephrine occurred on exercise after thyroidectomy the characteristic indexes of circulating epinephrine should be less evident after thyroidectomy. Standardized exercise by the same patient before and after operation has revealed that the response of the heart rate and blood pressure was usually the same or even greater.³²

The amounts of epinephrine which were injected in this investigation were presumably as large as or greater than amounts secreted under clinical conditions. With the doses usually employed pallor, tremor, palpitation and other signs of the action of epinephrine were manifest, and with slightly greater doses toxic and, at times, dangerous, reactions were encountered.

It is to be noted that although the response to epinephrine may not be changed appreciably when the basal metabolism falls to approximately minus 30 per cent following thyroidectomy a definitely increased response of the blood pressure, heart rate or consumption of oxygen may be obtained when the metabolism is raised by the administration of thyroid.¹² Further, myxedematous patients, after the basal metabolic rate has been brought to normal by thyroid medication, may show signs and symptoms of mild hyperthyroidism (cases 6 and 7).^{12a}

The effect on the metabolic rate is not the only or even the primary action of the active principle of the thyroid gland. Di-nitrophenol and di-nitro-ortho-cresol also are powerful metabolic stimulants, but there is no evidence that they possess any of the other "hormonal" actions of

32. Riseman, J. E. F.: The Relation of the Systolic Blood Pressure and Heart Rate to Attacks of Angina Pectoris Precipitated by Effort, to be published.

thyroid secretion.³³ In the absence of such artificial substances and such unphysiologic states the metabolic rate still affords the best single index of the degree of hypothyroidism. For the discussion in this paper of the sensitivity to epinephrine at different levels of hypothyroidism we have utilized both the metabolic rate and the clinical manifestations of myxedema as indexes of the hypothyroid state. That the thyroid and the adrenal glands have important interrelationships is not negated by our work. The level of hypothyroidism at which changes in this relationship may become evident is, however, below that maintained in our patients after thyroidectomy and so is of little or no significance in contributing to the therapeutic results of total thyroidectomy.

SUMMARY AND CONCLUSIONS

Studies of the sensitivity of the cardiovascular system of man to injections of epinephrine before and after total thyroidectomy are presented.

Three aspects of the physiologic action of epinephrine have been studied: (1) the sensitivity to epinephrine injected intravenously in patients with normal cardiovascular systems, angina pectoris or chronic cardiac failure; (2) the sensitivity to epinephrine of patients with various levels of basal metabolism, and (3) the rôle played by sensitivity to epinephrine in the improvement which occurs following total ablation of the thyroid gland in patients with angina pectoris or chronic heart disease.

Dilute solutions of epinephrine of known concentrations were injected by constant intravenous drip, and the responses of the blood pressure, heart rate, respiratory rate and depth, consumption of oxygen and blood sugar content were measured. Eighty-six studies were made in seventeen subjects.

The intravenous administration of epinephrine was followed by a definite and characteristic increase in the systolic blood pressure, heart rate, consumption of oxygen of the body, rate and depth of respiration and blood sugar content. The changes in diastolic blood pressure were variable and not great.

The responses to a given amount of epinephrine injected intravenously were strikingly similar when repeated measurements were made in a given subject under controlled conditions. The responses varied from person to person.

33. Dodds, E. C., and Robertson, J. D.: The Clinical Applications of Dinitro-Ortho-Cresol, *Lancet* **2**:1197, 1933. Cutting, W. C., and Tainter, M. L.: Comparative Effects of Dinitrophenol and Thyroxin on Tadpole Metamorphosis, *Proc. Soc. Exper. Biol. & Med.* **31**:97, 1933. Tainter, M. L.; Stockton, A. B., and Cutting, W. C.: Use of Dinitrophenol in Obesity and Relative Conditions, *J. A. M. A.* **101**:1472 (Nov. 4) 1933. Means, J. H., and Lerman, S.: The Action of Iodine in Thyrotoxicosis, *ibid.* **104**:969 (March 23) 1935. Unpublished observations on patients treated by total thyroidectomy.

The response of the systolic blood pressure was closely related to the rate of injection of epinephrine and was found to be the most valuable single index of the patient's sensitivity to epinephrine. The changes in heart rate, diastolic blood pressure, consumption of oxygen and measurements of respiration were not as directly related to the dose of epinephrine.

Patients with angina pectoris and those with congestive heart failure were not more sensitive to epinephrine than patients with no evidences of cardiovascular pathologic changes.

The sensitivity to epinephrine as measured by the aforementioned generally accepted indexes remained unchanged after total thyroidectomy so long as the basal metabolic rate was not lower than minus 30 per cent and the patient was free from distressing symptoms of myxedema.

When marked myxedema developed and the basal metabolic rate decreased below minus 30 per cent, a decreased response of the blood pressure and the heart rate to epinephrine became manifest in some instances.

The results of the present investigation show that the clinical improvement which followed total ablation of the normal thyroid gland is independent of any changes in the sensitivity to epinephrine, no alteration in the response to epinephrine being evident at the levels of hyperthyroidism maintained in our patients after operation.

Observations are presented which provide additional evidence that the relief from pain experienced by patients with angina pectoris immediately after total thyroidectomy, when there is no change in the basal metabolic rate or in sensitivity to epinephrine, is due to the interruption of sensory impulses from the heart to the central nervous system.

CIRCULATORY CHANGES IN ANGINA PECTORIS

AN EXPERIMENTAL STUDY

PHILIP SHAMBAUGH, M.D.*

BOSTON

The great majority of clinicians and investigators are now agreed on the essential pathologic physiology of angina pectoris, namely, that the attacks represent a transitory relative ischemia of a portion of the myocardium. There is, however, considerable doubt as to the mechanism of the production of the ischemia. Two fundamental possibilities present themselves: The supply of normal blood is inadequate for the needs of the heart muscle, or the composition of the blood is faulty, preventing a proper interchange of oxygen and metabolites. The latter possibility probably applies in only relatively few cases. The maintenance of an adequate supply of blood to the myocardium depends on two variable factors the demands of the myocardium and the ability of the blood vessels to meet this demand.

The factors which determine the ability of the blood vessels to meet the vascular demands of the myocardium are (1) the ability of the vessels to dilate as the demands of the heart muscle increase and (2) active vasoconstriction of the coronary arteries with or without an increase in the demands of the heart muscle. There is some doubt as to whether there is active vasoconstriction of the coronary arteries in man, although certain observations¹ suggest that it occurs. However, even if coronary spasm can and does occur as an etiologic factor in certain cases of angina pectoris, there are many cases of this disorder in which the postmortem condition of the coronary arteries is such as to make it highly improbable that the attacks of pain are due to transitory changes in the caliber of these vessels. In these cases it would seem more reasonable to suppose that the attacks are due to an increase in the demands of the heart muscle in the presence of an inability of the coronary vessels to meet this increased demand, because a narrowing or a rigidity prevents adequate vasodilatation.

In this group of cases one should look to the factors which increase the vascular demands of the heart muscle if one is seeking the precipitating cause of the individual attacks of pain. Such factors would be those which increase the heart rate or increase the vascular resistance

* Arthur Tracy Cabot Fellow.

From the Laboratory of Surgical Research, Harvard Medical School.

1. (a) Barbour, H. G.: The Constricting Influence of Adrenalin upon the Human Coronary Arteries, *J. Exper. Med.* **15**:404, 1912. (b) Anrep, G. W.: The Regulation of the Coronary Circulation, *Physiol. Rev.* **6**:596, 1926.

against which the heart must pump. It is a familiar observation that the usual conditions which bring on an attack of angina pectoris—physical exertion, exposure to cold and emotional upsets—are conditions generally associated with a rise in blood pressure and an increase in the heart rate. Moreover, the clinical observation that the attack of angina is frequently associated with a rise in blood pressure or heart rate, or both, has been well established. The fact, however, that this finding has not been invariable has led to a misinterpretation of the significance of these circulatory changes. It has been generally assumed that these changes are secondary phenomena caused by the pain and anxiety incident on the attack. However, as Christian² pointed out in commenting on the occurrence of attacks in which the pulse rate and blood pressure are found to be normal,

. . . of course it is possible that both changes occurred at or prior to the onset of the attack and had disappeared by the time some one could observe the pulse and blood pressure.

In recent years more careful observations have been made of the circulatory changes during the attack of angina pectoris. Wood and Wolferth³ reported observations on the blood pressure of fifteen patients during the attack of pain and found it definitely elevated in thirteen. In one of the two remaining cases, the blood pressure was observed to be 140 systolic and 100 diastolic, as compared with a previous reading of 150 systolic and 100 diastolic, but ten minutes after the attack it was found to have fallen to 125 systolic and 100 diastolic. Levine and Ernstene⁴ recently reported observations on twenty-three patients during spontaneous attacks and found that the blood pressure was definitely elevated in all of them. They stated the belief that the elevation is not due to the pain and suggested that the rise in blood pressure may, on the other hand, be the cause of the attack.

. . . the fact that in the subsidence of the attack, pressure levels need not go hand in hand with the disappearance of the pain, does not dismiss the possibility that the onset of the attack was actually produced by the increased pressure.

Levine stated that a fall in blood pressure during anginal attacks must be rare, and when it occurs one should suspect that an attack of coronary thrombosis is occurring, or that the pain is not anginal in character. In a careful clinical study of anginal attacks induced by exercise, Wayne and Laplace⁵ found an associated elevation of blood

2. Christian, H. A.: *Oxford Monographs on Diagnosis and Treatment*, New York, Oxford University Press, 1928, vol. 3, p. 244.

3. Wood, F. C., and Wolferth, C. C.: *Angina Pectoris*, *Arch. Int. Med.* **47**: 339 (March) 1931.

4. Levine, S. A., and Ernstene, A. C.: *Observations on Arterial Blood Pressure During Attacks of Angina Pectoris*, *Am. Heart J.* **8**:323, 1933.

5. Wayne, E. J., and Laplace, L. B.: *Observations on Angina of Effort*, *Clin. Sc.* **1**:103, 1933.

pressure and pulse rate. They agreed with Levine that the circulatory changes are more likely to be the cause than the result of the paroxysm. However, they concluded that the increased heart rate is more important than the elevated blood pressure in causing the attack, because they found the duration of the distress to be more closely correlated with the former.

A new approach to the problem of angina pectoris was provided by the consistent production of a definite pain response in dogs, mechanical interference with the coronary blood flow being employed. This was first demonstrated by Singer,⁶ in 1926, and was corroborated and enlarged on by Sutton and Lueth,⁷ who by an ingenious series of experiments showed that the pain response is due solely to the interference with the coronary blood flow and not to any adventitious factors incidental to the experimental procedure. These observations have since been corroborated by Percy, Priest and Van Allen⁸ and by White, Garrey and Atkins.⁹ White and his associates successfully used this response as a means of testing the effectiveness of various surgical procedures to interrupt the sensory pathways of the heart. The experimental procedure described by Sutton and Lueth consists in passing a suture about the anterior descending branch of the left coronary artery and bringing it out of the chest through a glass tube, about which the pericardium and thoracic wall are tightly closed. When the animal has fully recovered from the anesthesia, relatively slight traction on the coronary suture produces an almost immediate and unmistakable pain response, which ceases on the release of the traction.

Sutton and Lueth made observations of the blood pressure during this mechanical interference with the coronary blood flow with the animal under anesthesia and found that the blood pressure always showed a moderate fall. Wood and Wolferth³ made the same observation; in attempting to explain this discrepancy as compared with the rise in blood pressure generally seen in clinical anginal attacks, they stated:

The objection raised against the coronary hypothesis by these observations is not insurmountable. The blood pressure phenomena appearing during an experiment on an anesthetized animal cannot be expected to be reproduced exactly in a

6. Singer, R.: Experimentelle Studien über die Schmerzempfindlichkeit des Herzens und der grossen Gefässe und ihre Beziehung zur Angina Pectoris, Wien. Arch. f. inn. Med. **12**:193, 1926; **13**:157, 1927.

7. Sutton, D. C., and Lueth, H. C.: Pain, Arch. Int. Med. **45**:827 (June) 1930.

8. Percy, J. F.; Priest, W. S., and Van Allen, C. M.: Pain Due to Temporary Occlusion of the Coronary Arteries in Dogs, Am. Heart J. **4**:390, 1929.

9. White, J. C.; Garrey, W. E., and Atkins, J. A.: Cardiac Innervation, Arch. Surg. **26**:765 (May) 1933.

conscious man. The pressor reflexes set up by the pain of an anginal attack seem adequate to counteract a moderate fall of blood pressure due to a temporary myocardial ischemia.

None of these investigators have recorded blood pressure observations during the production of the pain response in the unanesthetized dog by this method. The following experimental study was undertaken in the hope of shedding light on the rôle of changes in the heart rate and blood pressure in attacks of angina pectoris.

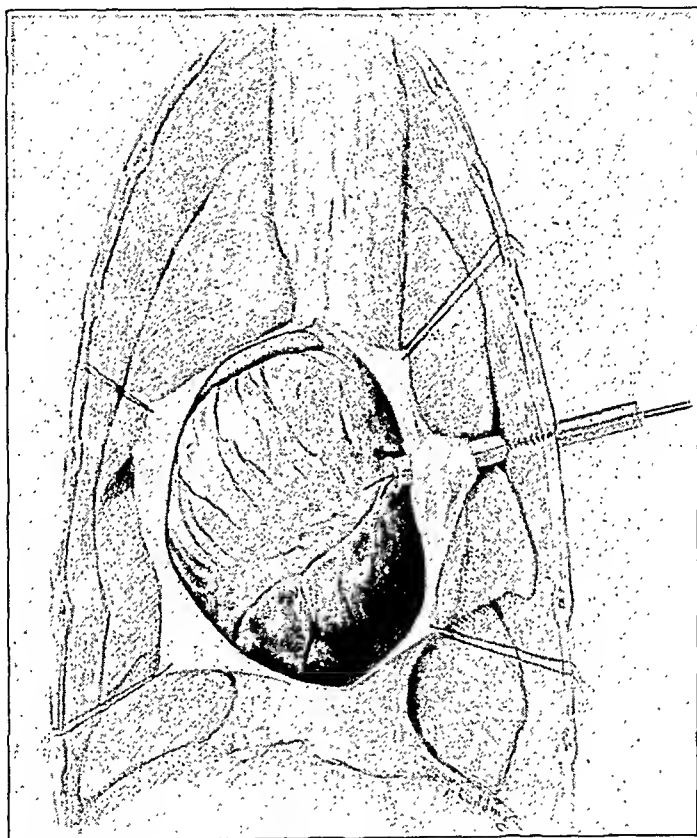


Fig. 1.—Drawing of a postmortem specimen, showing the coronary suture in situ.

METHOD

The procedure was essentially the same as that described by Sutton and Lueth. Under intratracheal ether anesthesia the left fifth rib was resected from the sternum to the midaxilla, and the pleura was opened. The pericardium was incised over the tip of the left auricle, which was displaced upward, exposing the proximal segment of the anterior descending branch of the left coronary vessels. An "E" silk suture was passed about the coronary vessels at this point by means of a blunt aneurysm needle after a small nick in the epicardium had been made to facilitate introduction. The suture was brought out of the chest through a flanged glass tube about which the pericardium and thoracic wall were tightly

closed, care being taken to remove the pneumothorax (fig. 1). The femoral artery was cannulated for blood pressure tracings, and provision was made for recording the respirations by means of a tambour. The ether was then withdrawn, the intra-tracheal tube removed and the animal allowed to recover from the anesthesia. From thirty to ninety minutes later the animal became sufficiently alert to respond in the typical manner to traction on the coronary suture. In all of the cases the inclusion of the coronary artery by the suture was corroborated by postmortem dissection. In some of the experiments the arterial cannula was withdrawn, the animal was removed from the operating table for recovery, and no effort was made to record the blood pressure during the subsequent observations. When epinephrine was used, the dilutions were made with distilled water just before the test. The

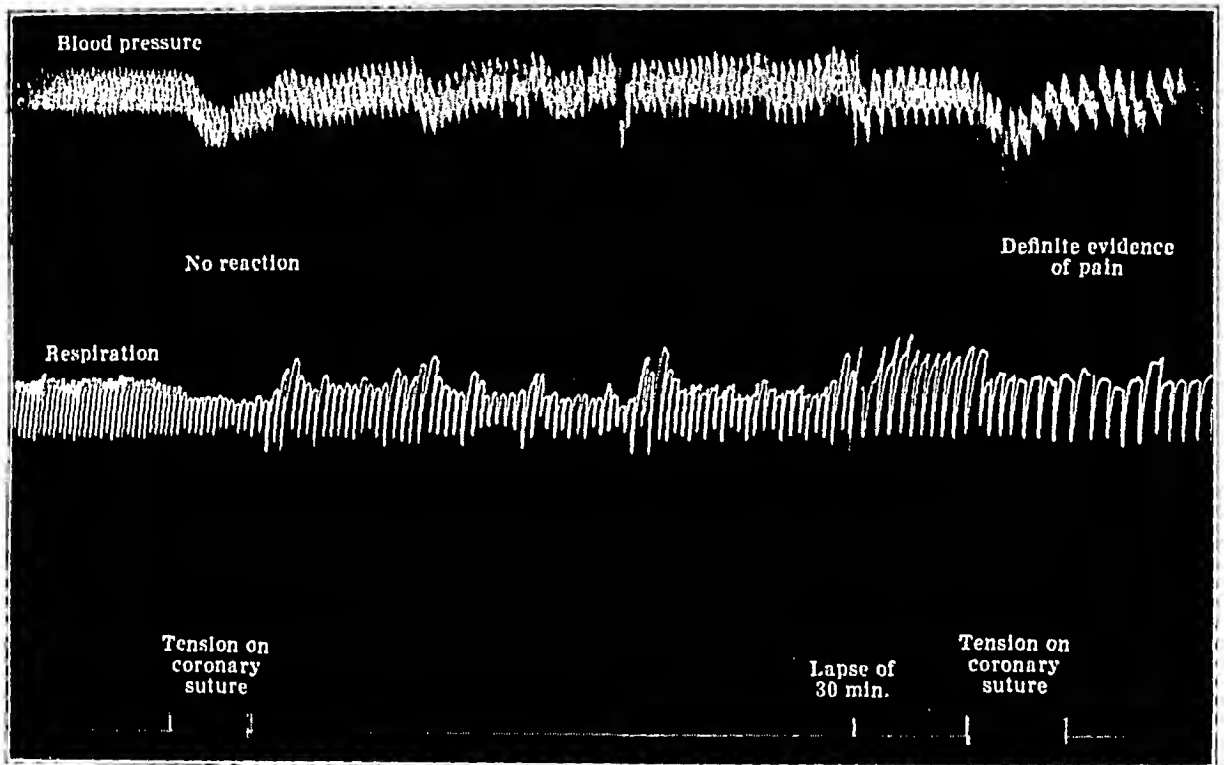


Fig. 2.—Tracing from dog C9, showing the blood pressure reaction to traction on the coronary suture before and after recovery from anesthesia.

dosages of epinephrine were measured accurately in a tuberculin syringe, and the rate of injection was carefully timed.

OBSERVATIONS

Effect of Experimental Angina Pectoris on the Blood Pressure.—The effect of interfering with the coronary blood flow in four dogs was observed before and after recovery from the anesthesia. While the dog was still anesthetized a slight fall in blood pressure was invariably noted. After recovery from the anesthesia, when traction on the coronary suture evoked a definite pain reaction, the blood pressure still showed a slight fall in most cases (figs. 2 and 3). There was no

appreciable variation in a few experiments, and in several a slight rise was observed (fig. 4). In no case did a significant rise of blood pressure occur (table). A definite variation in the heart rate occurred during traction on the coronary suture, but this was always a slowing, which was particularly marked when the traction was first applied and which frequently caused a sharp transitory fall in blood pressure. No change was noted in this reaction after recovery from the anesthesia; there was therefore no evidence that the discomfort tended to cause tachycardia.

The fact that a rise in blood pressure was never observed during traction on the coronary suture while the animal was under anesthesia,

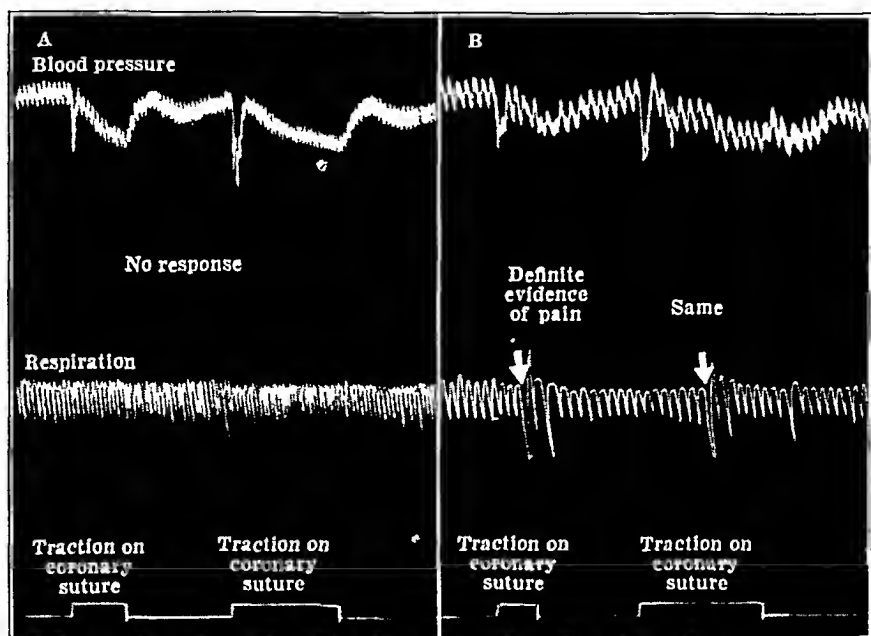


Fig. 3.—Tracing from dog C6, showing the blood pressure reaction to traction on the coronary suture (A) before recovery and (B) after recovery.

whereas a slight rise was occasionally seen when the test was repeated after recovery, suggests that the pain reaction may in several instances have caused this rise. However, there was no relation between the degree of the objective response of the dog and these minor variations in the blood pressure reaction, and the rise was so slight when it occurred that I believe that it cannot account for the rather striking elevation frequently seen in clinical attacks of angina. Moreover, I accidentally had the opportunity to observe the blood pressure reaction to pain of a different origin when on two occasions a small amount of 20 per cent citrate solution used in the arterial cannula flowed back into the artery, causing an unexpected pain reaction of considerable severity requiring reetherization. There was no rise in blood pressure

with even this severe reaction (fig. 5). In this connection it is interesting to recall the clinical observation by Levine⁴ that the blood pressure remained unaltered during two severe attacks of renal colic in a patient who was subject to attacks of angina pectoris.

Effect of Elevation in the Blood Pressure on the Production of Experimental Angina Pectoris.—The production of a pain response by Sutton and Lueth's method depends on a mechanical constriction of the coronary vessels. This reproduces the mechanism in clinical angina pectoris only so far as one assumes an active vasoconstriction as a cause of the attacks. This factor has not been proved and is highly questionable in many cases. Therefore I endeavored to precipitate the

Change in Blood Pressure with Traction on the Coronary Suture

Dog	Initial Pressure, Mm. Hg	Observations Before Recovery from Anesthesia, Mm. Hg	Observations After Recovery and in Presence of Pain Reaction, Mm. Hg
C 6	130	Fall, 18 Fall, 16	Fall, 20 Fall, 28 Fall, 10 Fall, 14 Fall, 6
C 380	144	Fall, 6 Fall, 4	Rise, 8 No change Rise, 6 Fall, 8
C 9	148	Fall, 18 Fall, 10	No change No change Rise, 6 Fall, 6 Rise, 10
C 10	140	Fall, 16	Fall, 18 Fall, 10 Fall, 16 Fall, 10

typical pain reaction in dogs by increasing the myocardial demands and keeping the coronary blood flow relatively constant. This was successfully accomplished by maintaining a steady subminimal traction¹⁰ on the coronary suture by means of weights suspended over pulleys (fig. 6) and then sharply increasing the circulatory load on the heart by injecting epinephrine into the femoral vein.

Dog C 364.—The animal was given 30 mg. of morphine and ether intratracheally on Nov. 29, 1933. The left fifth rib was resected, and the suture placed around the anterior descending branch of the left coronary vessels and brought out through the glass tube. The wound was closed.

Four hours later the dog was active and alert. Traction on the coronary suture produced an immediate response characterized by a stiffening of the fore-

10. The term subminimal traction is used to describe the pull which is just less than that required to elicit the discomfort reaction.

legs and increased respiration and restlessness. An intravenous injection of 0.5 cc. of a 1:10,000 solution of epinephrine caused no evidence of discomfort. A constant traction was now maintained on the coronary suture by means of weights

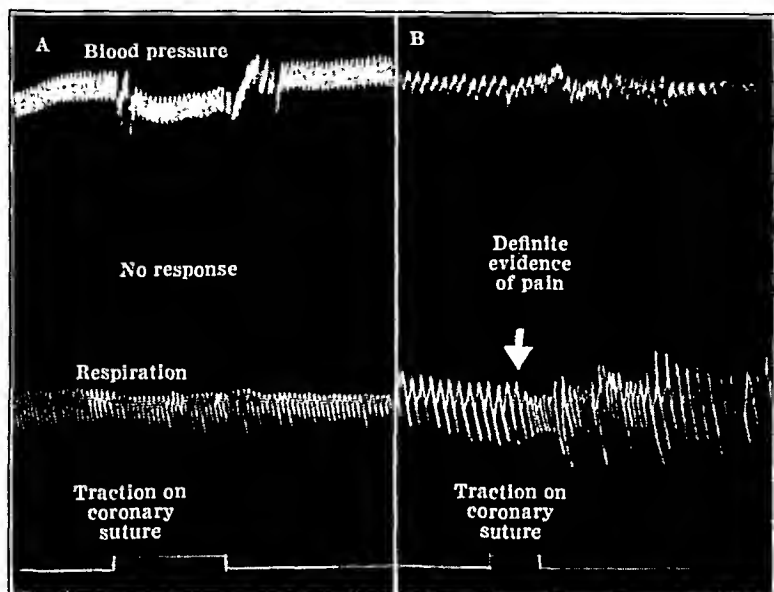


Fig. 4.—Tracing from dog C12, showing the blood pressure reaction to traction on the coronary suture (A) before recovery and (B) after recovery.

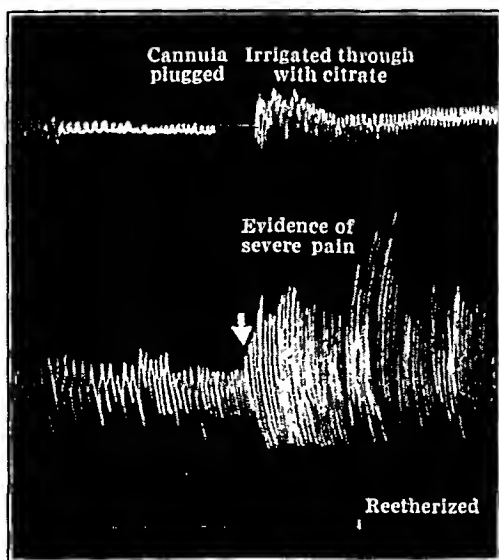


Fig. 5.—Tracing from dog C9, showing no appreciable change in the blood pressure in the presence of a severe pain response.

(100 Gm.) suspended over pulleys, the tension being so adjusted as to be less than that required to produce pain. The aforementioned dose of epinephrine was now repeated and within from ten to fifteen seconds there was a sudden pain reaction, similar, though more severe, than that produced previously by direct

traction on the coronary suture. The pain was relieved by a release of the traction. After a rest of five minutes, during which epinephrine alone again produced no evidence of discomfort, this procedure was repeated; the constant moderate traction was maintained for from three to four minutes without discomfort, following which the same dose of epinephrine was again followed almost immediately by the unmistakable pain reaction.

Dog C 360.—On Dec. 3, 1933, this animal was prepared like dog C 364. Four hours later it was completely recovered and alert. The femoral artery was cannulated under local anesthesia, and tracings of blood pressure and respiration were recorded on a smoked drum. Traction on the coronary artery evoked the typical response with increased respiratory rate but no significant change in blood pressure. Five-tenths cubic centimeter of a 1:10,000 solution of epinephrine administered

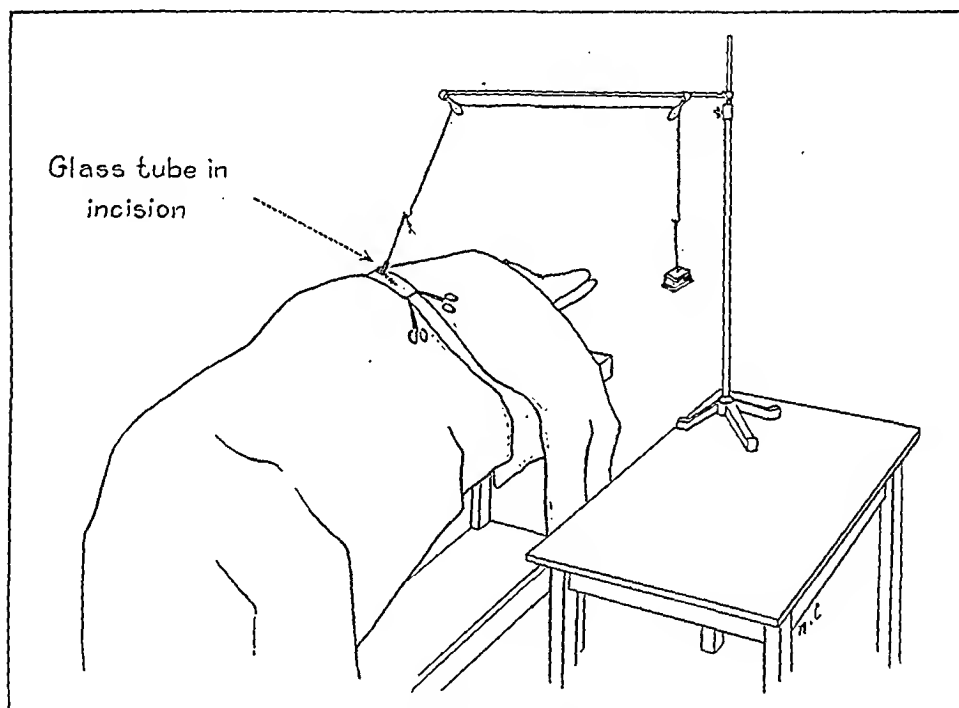


Fig. 6.—Diagram of the apparatus for maintaining constant traction on the coronary suture.

intravenously caused a sharp rise in blood pressure but no evidence of discomfort and no respiratory change. A constant traction of 100 Gm. was applied to the coronary suture without evidence of discomfort. Injection of the same dose of epinephrine was now followed by definite evidence of pain with an increase in respiratory rate, relieved by release of the pull (fig. 7). The same procedure was repeated after ten minutes, again producing the definite pain response.

Dog C 9.—On Jan. 12, 1934, the animal was prepared as were the other animals. It was alert and responsive forty minutes after the cessation of ether. A typical response was elicited by traction on the coronary suture. Two-tenths cubic centimeter of a 1:1,000 solution of epinephrine administered intravenously caused a rise in blood pressure but no discomfort. Constant traction of 100 Gm. was applied to the suture without discomfort. The same dose of epinephrine was then

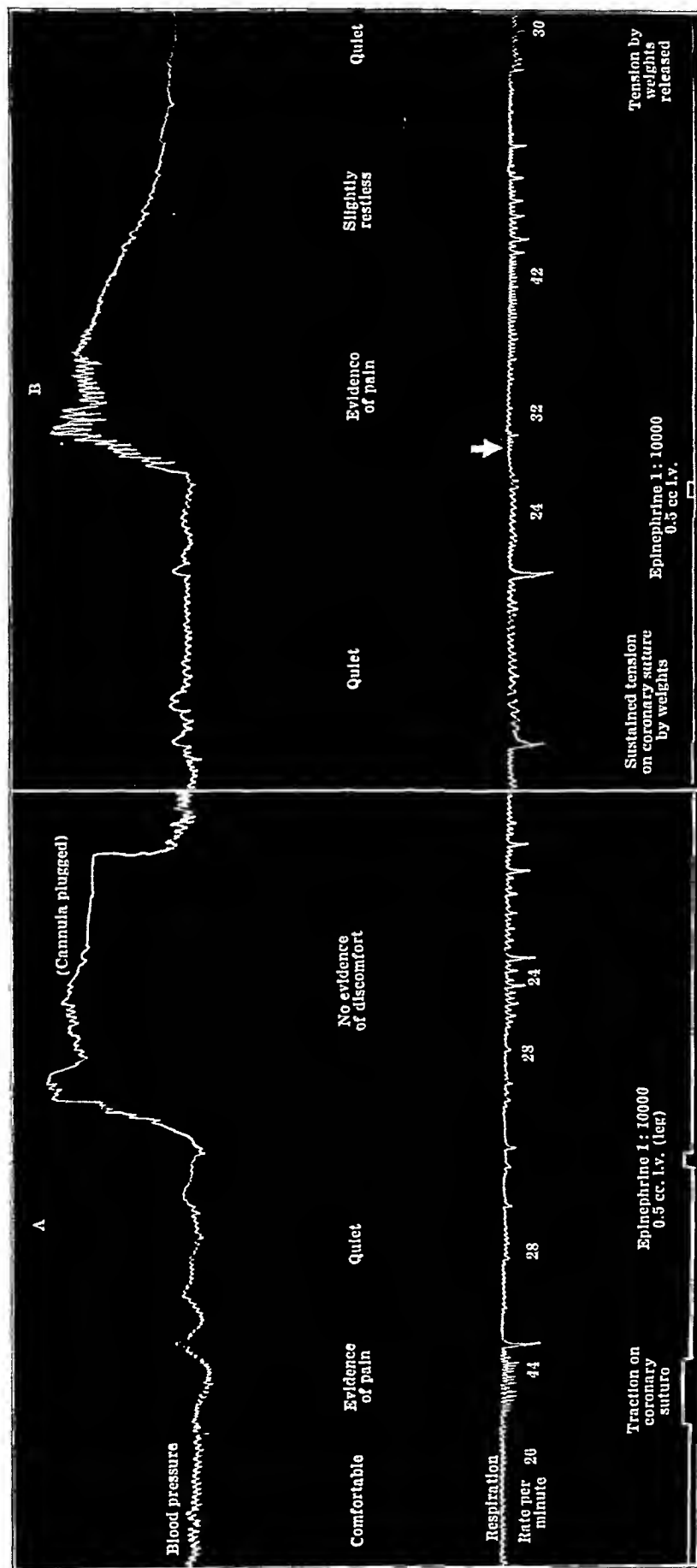


Fig. 7.—The tracing from dog C360. *A* shows no response to epinephrine alone, and *B*, a positive response to epinephrine with subminimal traction on the coronary suture.

repeated, and a definite pain reaction (fig. 8) was obtained. The injection of epinephrine was repeated without the traction, and again there was not the slightest evidence of discomfort.

Dog C 12.—On Feb. 26, 1934, the animal was prepared like the others. A prompt, typical reaction to traction on the coronary suture was elicited thirty minutes after the cessation of ether. One-tenth cubic centimeter of a 1:1,000 solution of epinephrine administered intravenously produced a satisfactory rise in blood pressure without evidence of discomfort. Constant traction of 120 Gm. was applied to the coronary suture without discomfort. The injection of epinephrine was now repeated with a definite pain response at the height of the vasopressor reaction (fig. 9).

Dog C 29.—On March 20, 1934, the animal was prepared as usual. The vasopressor response to various doses of epinephrine was determined, following which

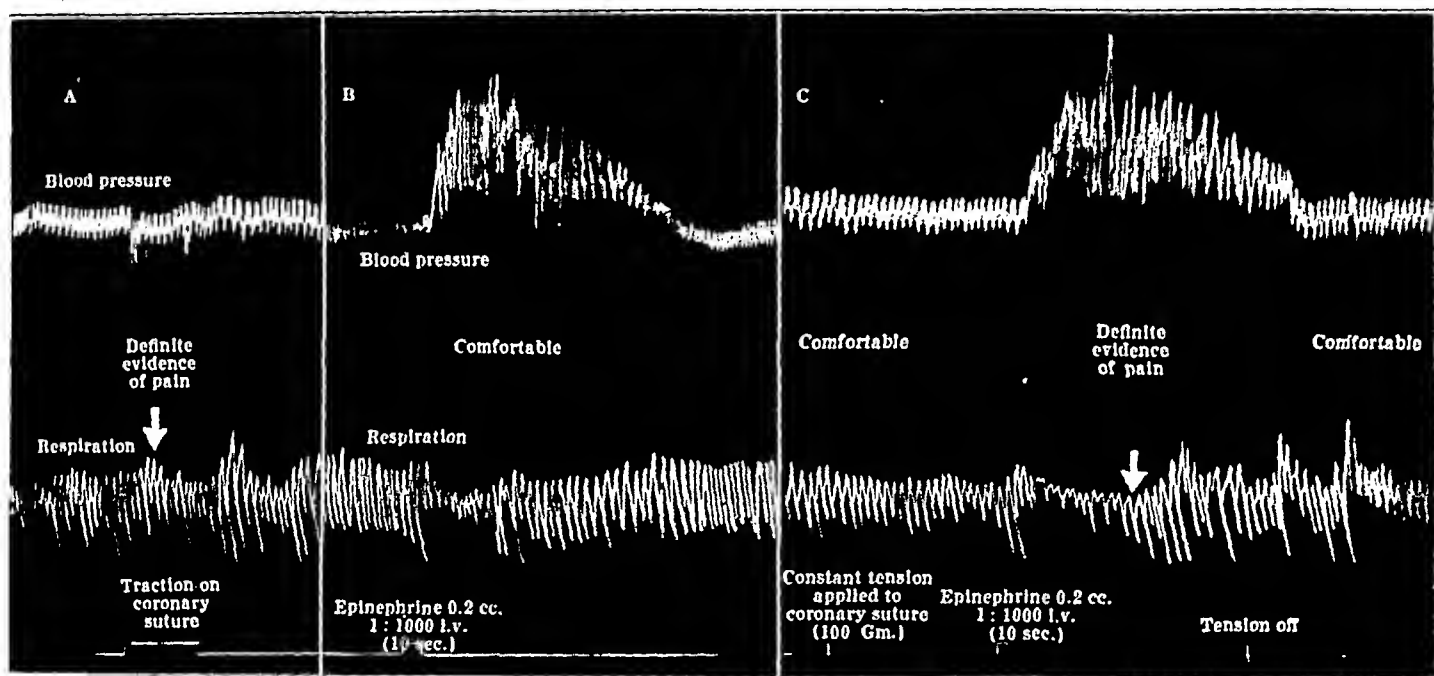


Fig. 8.—Tracing from dog C9. *A* shows the typical reaction to traction on the coronary suture; *B*, absence of response to epinephrine alone, and *C*, a typical response to epinephrine, with subminimal traction on the coronary suture.

the arterial cannula was removed and the animal allowed to recover from the anesthesia. Observations were made one-half hour later, only the respirations being recorded. Traction on the coronary suture produced the typical response. Four-tenths cubic centimeter of a 1:10,000 solution of epinephrine administered intravenously was given without discomfort. A constant traction of 100 Gm. was applied to the coronary suture without causing discomfort. Increasing doses of epinephrine were then injected without a reaction until 0.2 cc. of a 1:10,000 solution was reached. This injection was followed in thirty seconds by the definite typical reaction which subsided spontaneously after forty-five seconds, although the traction was maintained. The onset and duration of the response were found to correspond fairly closely to the previously determined vasopressor reaction to the same dose of epinephrine. A larger dose of epinephrine (0.4 cc. of a 1:10,000 solution) was followed by a definitely severer reaction, which was relieved by

cessation of the traction. As a final control, 0.5 cc. of a 1:10,000 solution of epinephrine was injected without the constant traction, and no response was obtained (fig. 10).

Dog C 288.—On March 21, 1934, the animal was prepared by the usual procedure. The vasopressor effect of varying doses of epinephrine was determined, the arterial cannula was removed and the animal allowed to recover. Four hours later it responded in the typical fashion to traction on the coronary suture. One-tenth cubic centimeter of a 1:1,000 solution of epinephrine administered intravenously caused no discomfort. Constant tension of 100 Gm. was applied to the coronary suture and maintained without causing discomfort. The same dose of epinephrine was then followed in fifteen seconds by the typical reaction.

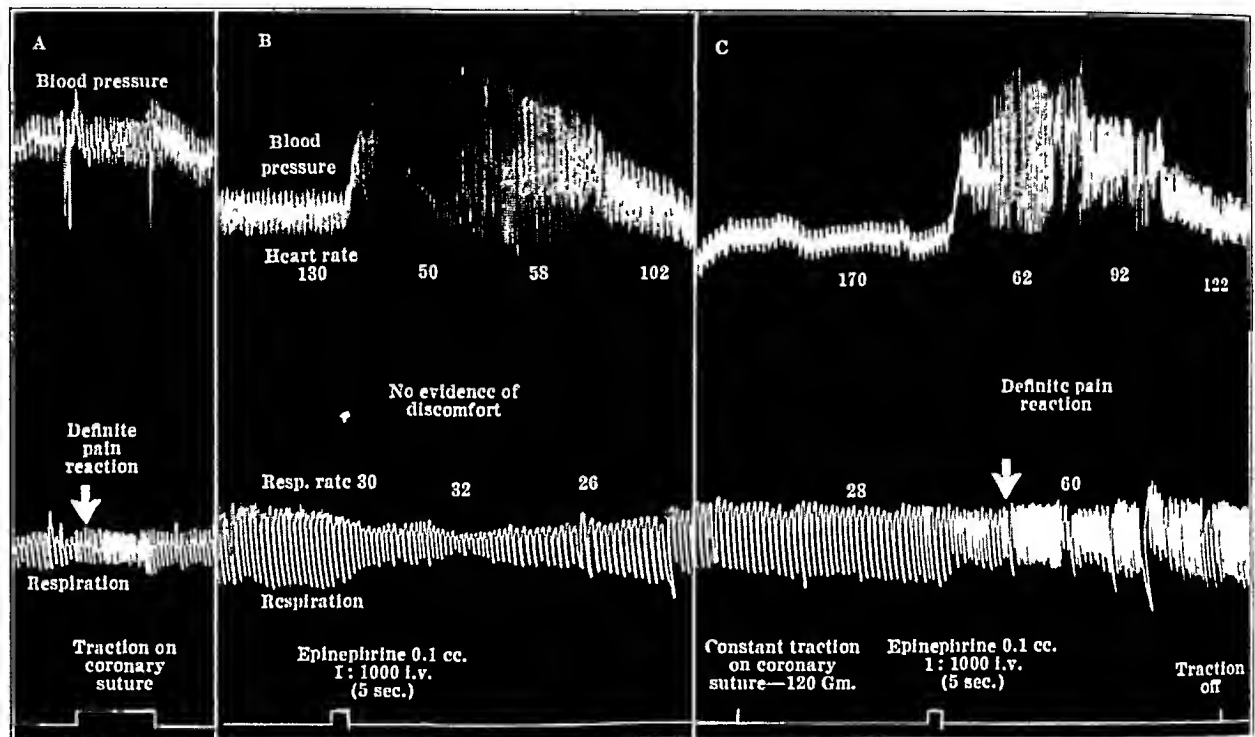


Fig. 9.—Tracing from dog C12. *A* shows the typical reaction to traction on the coronary suture; *B*, absence of response to epinephrine alone, and *C*, a typical response to the same dose of epinephrine, with subminimal traction on the coronary suture.

I was unsuccessful in seven experiments. In three of these pain in the leg inadvertently produced by the citrate solution¹¹ necessitated immediate reetherization and termination of the observations. Two dogs were too restless for accurate observations, and in two dogs no reaction was produced by subminimal traction and epinephrine, in spite of good cooperation. The failure in these two experiments is not sur-

11. A rather strong solution of sodium citrate (20 per cent) had been used. This was later abandoned for a sodium sulphate solution, one-half saturated.

prising in view of the difficulties involved in establishing a constant constriction of the coronary vessels, which of itself is not sufficient to cause pain but which so obstructs the coronary blood flow as to cause an insufficient supply of blood when the demands of the myocardium are suddenly increased.

Three possible mechanisms are to be considered in attempting to explain the production of pain by the injection of epinephrine, as described earlier: 1. There is an active vasoconstriction of the coronary artery which, superimposed on the already existing subminimal mechanical constriction, is sufficient to produce the myocardial ischemia and the consequent pain response. This factor may be dismissed in view of the general agreement among physiologists that epinephrine dilates rather than constricts the coronary arteries in the dog.^{1b} 2. There is a resulting tachycardia which increases the vascular demands of the myocardium, and these demands cannot be adequately supplied in view of the mechanical constriction of the coronary vessels. This factor did not obtain in these experiments, however, as the dosage of epinephrine used caused a slowing of the heart, which was at times marked (fig. 9), but never an acceleration. 3. The rise in blood pressure increases the work of the heart, thus increasing the vascular demands of the myocardium, which are not adequately supplied. This appears to be the most probable explanation, for in none of the experiments could the pain reaction be produced by a dosage of epinephrine insufficient to cause a fairly good rise in blood pressure (fig. 10). It seemed advisable, however, in view of the recent observations by Wayne and Laplace,⁵ to try to produce this pain reaction by accelerating the heart rate without raising the blood pressure; experiments were therefore undertaken with this in view.

Effect of Increasing the Heart Rate on the Production of Experimental Angina Pectoris.—I first attempted to increase the heart rate by sectioning the vagi, which had been previously mobilized, but this was found to disturb the dog too much for subsequent accurate observations. Atropine was found to be satisfactory, as it causes a marked tachycardia which occurs within a few seconds after intravenous injection but no elevation of blood pressure (fig. 11). However, the tachycardia, which is due to paralysis of the vagus, persists for a number of hours; therefore the observation of the effect of suddenly increasing the heart rate in the presence of a subminimal traction on the coronary suture could be carried out only once during a given experiment.

Dog C 8.—On March 23, 1934, the animal was prepared as in previous experiments, and the vasopressor response to varying dosages of epinephrine was determined while the dog was still under anesthesia. The cannula was removed, and the dog was allowed to recover. Four hours later, a prompt, typical response

was obtained by pulling on the coronary suture. A constant traction of 100 Gm. was applied to the suture without evidence of discomfort. Increasing doses of epinephrine were then injected without response, until 0.2 cc. of a 1:1,000 solution was reached, which produced the typical reaction relieved by releasing the pull. After a rest of five minutes the same subminimal constant traction was again applied and then both 0.1 cc. of a 1:1,000 solution and 0.2 cc. of a 1:1,000 solution failed to precipitate the pain reaction. With the traction still in place, 0.54 mg. of atropine sulphate dissolved in 4 cc. of distilled water was given intravenously, followed by a sudden increase in the heart rate from 128 to 200 per minute, coming on within fifteen seconds after the injection. There was no indication of discom-

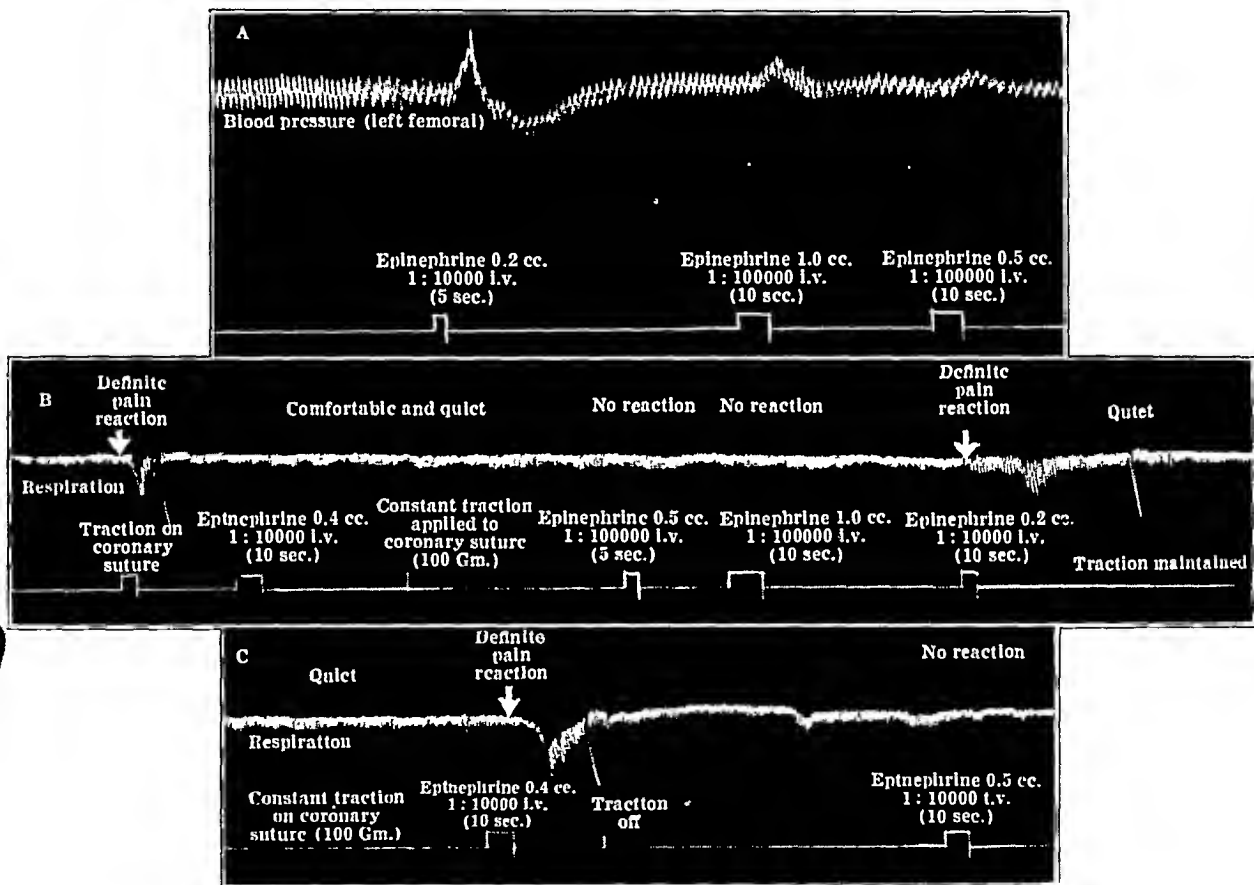


Fig. 10.—Tracing from dog C29. *A* shows the vasopressor response to various doses of epinephrine; *B*, the typical reaction to traction on the coronary suture, failure to respond to epinephrine alone, maintenance of constant subminimal traction without discomfort and a positive reaction to epinephrine in the presence of this constant traction, and *C*, a more severe reaction to a larger dose of epinephrine in the presence of the same constant traction, immediate relief by release of traction and absence of reaction after a final control injection of epinephrine.

fort. However, the dose of 0.1 cc. of a 1:1,000 solution of epinephrine, which twice previously had failed to produce the response, was now followed by a marked and typical reaction (fig. 12).

Dog C 70.—On March 28, 1934, the animal was prepared according to the usual procedure. Four hours later it responded in the usual manner to traction

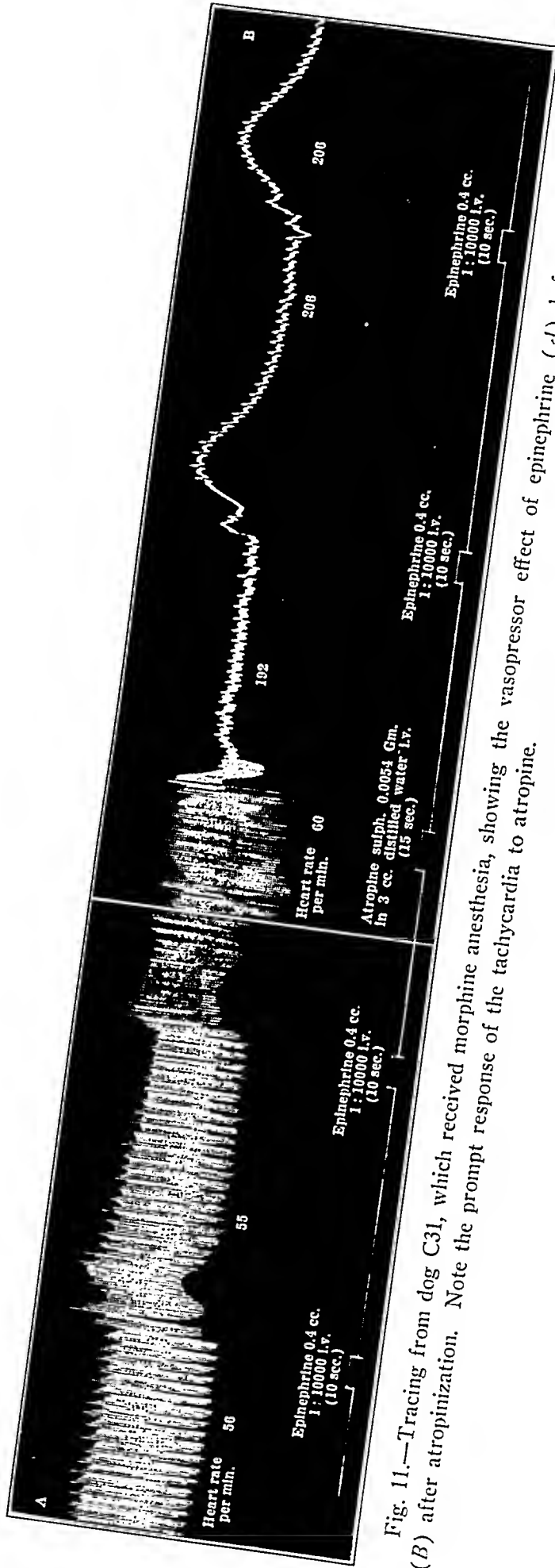


Fig. 11.—Tracing from dog C31, which received morphine anesthesia, showing the vasopressor effect of epinephrine (A) before atropinization and (B) after atropinization. Note the prompt response of the tachycardia to atropine.

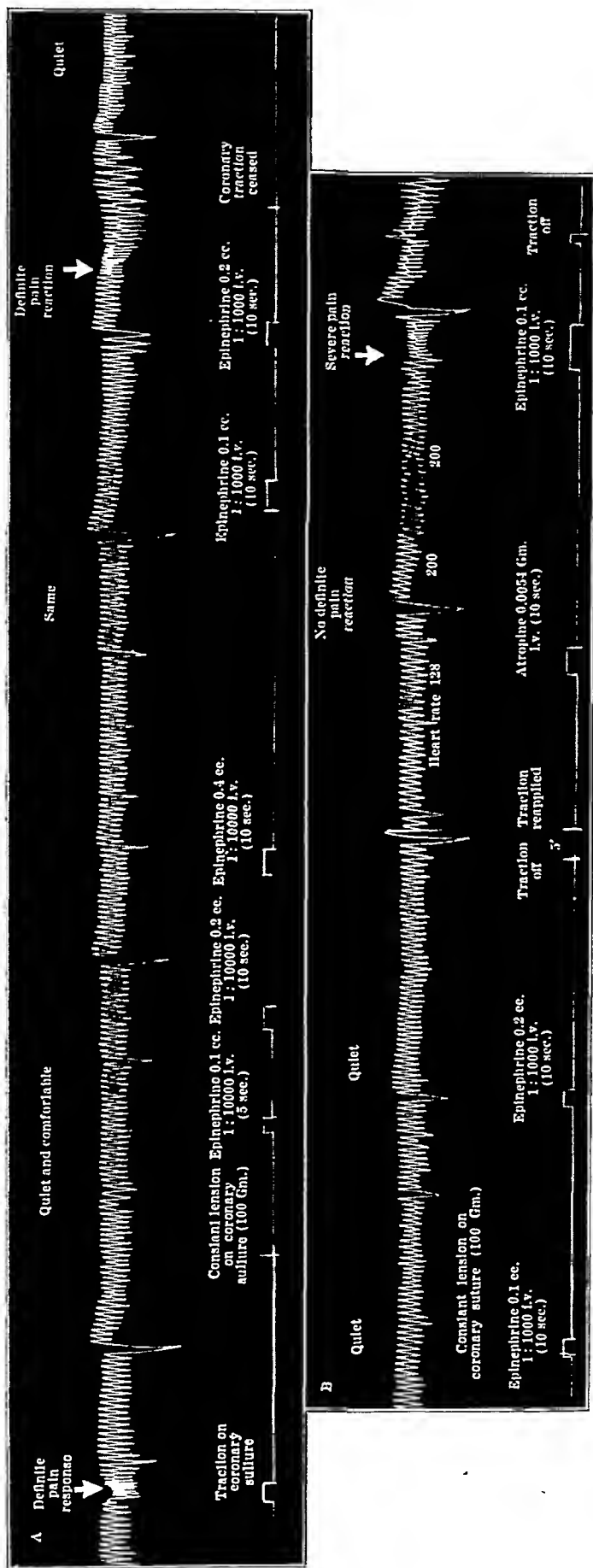


Fig. 12.—Tracing from dog C8. A shows the typical reaction to traction on the coronary suture, the maintenance of constant traction without discomfort, a positive reaction to epinephrine when a satisfactory vasopressor dose was reached and relief from discomfort on cessation of the traction, and B, no response to atropine in the presence of the subminimal traction and an increased reaction to epinephrine after atropinization.

of the experiment, for on several occasions an unmistakable pain response with whining and stiffening of the forelegs was observed with no change in the respirations (figs. 2 and 7). The important observation in the foregoing studies, therefore, is the note made at the time of the experiment as to the objective reaction of the animal. The changes in the respiratory tracings are merely confirmatory and in addition serve to record the time relations of the response. When the respiration is altered with the pain reaction, and this is the rule, I have found that an acceleration is a more accurate indication than is an increase in amplitude. In this connection I wish to emphasize the fact that in no case was the animal allowed to suffer unnecessarily. As soon as the definite typical response had occurred, the traction was immediately terminated, with prompt relief of the discomfort. It was found unnecessary to carry the stimulus beyond the point at which a moderate degree of discomfort was produced.

These experimental observations lend support to the clinical concept that the elevation of blood pressure frequently observed in angina pectoris is more likely the cause than the result of the attack. The tachycardia may also play a similar rôle, although I have not been able to demonstrate this in my experiments with animals. The fact that these circulatory changes may precipitate attacks in certain cases of angina pectoris does not mean that they are the important factors in all cases of this disorder.

SUMMARY

Experimental evidence is presented to show that in the dog cardiac pain produced by mechanical constriction of the coronary vessels does not cause a significant rise in blood pressure. On the other hand, the pain response can be precipitated by suddenly raising the blood pressure in the presence of a subminimal constriction of the coronary vessels.

ACUTE CARDIAC INFARCTION INVOLVING ANTERIOR AND POSTERIOR SURFACES OF LEFT VENTRICLE

ELECTROCARDIOGRAPHIC CHARACTERISTICS

CHARLES CHRISTIAN WOLFERTH, M.D.
AND

FRANCIS CLARK WOOD, M.D.

WITH THE COLLABORATION OF SAMUEL BELLET, M.D.
PHILADELPHIA

Twenty of our cases of acute coronary occlusion have come to necropsy during the past three years. In every instance the location of the infarct, predicted on the basis of the electrocardiogram, has been confirmed.¹ This would indicate that when chest leads are used as well as limb leads the position of an acute infarct can be determined with considerable accuracy. The localizing signs of typical anterior and typical posterior lesions have been described in a previous paper.² Moreover, the prognostic difference between the groups, mentioned in that paper, has been confirmed by further observations.¹

Certain factors may confuse the observer in attempting to locate the lesion: 1. The infarct may occur in some unusual position, as in the lateral wall of the left ventricle or in the right ventricle. The localizing signs of such lesions are not definitely established as yet. 2. The patient may have had a previous cardiac infarct. However, in our experience this has not prevented the localization of a recent lesion.³ 3. Ten cases have occurred in our series of 104 in which contradictory signs have appeared. In this group there have been electrocardiographic indications of acute lesions in both the anterior and the posterior wall of the left ventricle. In some cases the tracing has suggested that the main lesion was anterior (case 1), and in others, that the main infarct was posterior (case 2). Two of the 10 cases have come to necropsy. The pathologic examination in each instance revealed a lesion involving part

From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

1. Wolferth, C. C.; Wood, F. C.; Bellet, S., and Edeiken, J.: The Electrocardiographic Diagnosis of Coronary Occlusion with Chest Leads, *Tr. A. Am. Physicians* **49**:223, 1934.
2. Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Diagnosis of Coronary Occlusion: Further Observations on the Use of Chest Leads, *Arch. Int. Med.* **52**:752 (Nov.) 1933.
3. Wood, Bellet, McMillan and Wolferth,² cases 3 and 33.

of both the anterior and the posterior wall of the left ventricle. Consequently, in this paper, an attempt has been made to analyze the electrocardiographic findings in this group and to outline the signs of acute anteroposterior cardiac infarction.

CASE 1.—J. L., a white man aged 52, had noticed undue dyspnea on effort since January 1933. On Dec. 11, 1933, at 10 p. m., while playing with his children, he experienced an intense deep-seated pain beneath the sternum which spread to the precordium and radiated to the left shoulder. A feeling of suffocation accompanied the pain. He became nauseated and subsequently vomited. Morphine gave some relief, but his suffering continued through the night and the next morning. He was admitted to the Hospital of the University of Pennsylvania in the service of Dr. Alfred Stengel at noon on December 12.

Examination at that time revealed: temperature, 98 F.; pulse rate, 90, and respiratory rate, 28. The blood pressure was 120 systolic and 75 diastolic. The patient appeared acutely ill. He was somewhat irrational, orthopneic and cyanotic. No abnormalities of the heart sounds were noted. There were many râles at the base of the right lung. The leukocyte count was 20,000.

The next day the temperature rose to 101 F.; the heart sounds became more distant. The blood pressure dropped to 100 systolic and 65 diastolic. The pain persisted with occasional remissions. On December 14 it subsided. On December 17 the temperature was normal and the leukocyte count was 11,800. On December 21 fever recurred, and pain in the right side of the chest appeared. On December 26 at 7:30 a. m. the patient suddenly collapsed and died.

Necropsy was performed by Dr. John Parsons on December 26. The left anterior descending coronary artery was obstructed by a recent thrombus 1.5 cm. from its origin. The other coronary arteries were relatively free from sclerosis. None were stenosed or obstructed. The circumflex branch of the left coronary artery was unusually large. Its point of origin was above the thrombus. There was a large infarct involving the lower half of the anterior surface of the left ventricle, the apex and the lower 3 cm. of the posterior surface of the left ventricle. The entire apex of the heart was necrotic. The interventricular septum was almost completely infarcted and was in a state of liquefaction necrosis. A large mural thrombus was found in the left ventricle. The base of the right lung disclosed a recent infarct.

The electrocardiograms are shown in figure 1. The first, taken on December 13, showed left bundle branch block. There were deviations of the RS-T interval in leads IV and V. However, in the presence of the bundle branch block we did not know whether or not these deviations of the RS-T interval signified acute cardiac infarction. By December 15 the bundle branch block had disappeared, and lead IV showed the typical signs of a recent infarct in the anterior wall.² The deviation of the RS-T interval in lead V was somewhat less than that in lead IV. Lead VI showed a slight elevation of this interval. The limb leads showed a small elevation of the RS-T interval in all leads, most marked in lead II. The third tracing, taken on December 18, showed some diminution in the deviations of the RS-T interval. The last tracing, taken on December 2, showed a return of the limb leads to normal. The chest leads still showed evidence of the acute myocardial lesion.

Summary.—The case was one of coronary occlusion showing electrocardiographic signs of acute anterior infarction and certain indications that the lesion extended to the posterior surface of the heart (table 2)

and to the interventricular septum (bundle branch block). Necropsy confirmed the electrocardiographic localization.

CASE 2.—H. F. was a bricklayer aged 59. Prior to the present illness he was known to have had elevated blood pressure. He had not suffered anginal pain. On Sept. 19, 1933, he experienced an attack of substernal oppression which was partly relieved by soda. For the next nine days he felt "out of sorts" and had occasional mild pains in the chest. On October 28 he suffered a severe, prolonged attack of substernal pain, vomited, collapsed and thought he was going to die. He was admitted to the Mount Sinai Hospital on October 30 in the service of Dr. Rubenstone. Pain was still present. Cyanosis was noted. The blood pressure was 100 systolic and 65 diastolic. The temperature was 99 F.; the pulse rate was 60, and the respiratory rate was 30. The heart was described as "enlarged to the left." A soft systolic murmur was heard at the apex. The heart sounds were muffled. A tentative diagnosis of acute coronary occlusion was made.

The temperature remained elevated until November 14. Leukocytosis (from 10,400 to 13,400 cells) appeared. The blood pressure remained about 100 systolic and 60 diastolic. Two other attacks of pain occurred, on November 6 and on December 26. The latter was accompanied by elevation of the temperature. The value for blood sugar was elevated (from 150 to 300 mg. per hundred cubic centimeters) throughout the patient's stay in the hospital. The urine showed a small amount of sugar from time to time. Insulin was administered once.

On Jan. 12, 1934, signs of a pleural effusion on the left side were noted. On January 19, 800 cc. of yellowish fluid was removed from the pleural cavity on the left side. The fluid reaccumulated, and tapping was necessary on five occasions. The patient gradually went downhill. The pulse rose to 100. The blood pressure dropped to 90 systolic and 60 diastolic. Pallor, cyanosis and cough were noted. On February 16 a fluoroscopic study of the function of swallowing revealed "slight obstruction to the passage of barium in the lower end of the esophagus. The capsule also passed with difficulty. We believe this partial obstruction to be due to the pressure of an extremely enlarged heart." The patient died suddenly on March 6.

Necropsy was performed on March 7. The right coronary artery was completely occluded on the posterior surface of the heart 5 cm. from its origin. The left anterior descending artery showed marked sclerosis. The lumen of this vessel was considerably narrowed at several points. The circumflex branch of the left coronary artery was completely occluded 5 cm. from its origin and was converted into a solid cord beyond this point. A large aneurysm protruded from the posterior surface of the left ventricle which measured 8 cm. in diameter and 8 cm. in depth. Many thrombi were found in the aneurysm. There was marked sclerosis of the lower third of the anterior surface of the left ventricle. The scarring of this region was continuous with the lesion on the posterior surface.

Electrocardiograms were taken on Oct. 31, Nov. 1, 7 and 14 and Dec. 4, 6, 11, 14, 18, 21 and 26, 1933, and on Jan. 10 and 24 and Feb. 23, 1934. Two of these tracings are shown in figure 2 *A*. The first, taken on October 31, showed elevation of the RS-T interval in all three limb leads, most marked in lead II. A deep Q wave was present in lead III. Lead IV showed a depression of the RS-T interval. The initial downward deflection of the QRS complex was preserved. Lead V was within normal limits. Lead VI showed an elevation of the RS-T interval. The second tracing (fig. 2 *A2*), taken on December 18, showed the signs of healed infarction of the posterior wall.²

In this case the pathologic evidence was less direct than in case 1 because four months elapsed between the attack and the postmortem examination. However, a lesion involving both the anterior and the posterior surface of the left ventricle was found at necropsy. Therefore it seems probable that on October 31 when the first tracing was taken, both the anterior and the posterior surface of the left ventricle were the seat of acute infarction.

Summary.—The case was one of coronary occlusion which on October 30 showed electrocardiographic evidence of acute infarction in both anterior and posterior surfaces of the left ventricle. The tracings taken subsequently suggested that the main lesion was situated posteriorly. Necropsy four months after the acute attack supported the electrocardiographic localization of the lesion.

Eight other cases have occurred in our series in which the electrocardiographic studies suggested acute infarction of both the anterior and the posterior wall of the left ventricle. Since pathologic confirmation of the location of the lesion was not possible in these 8 cases, they will not be reported in detail. The pertinent data concerning them are summarized in table 1.

The typical phenomena of the RS-T interval produced by the acute anteroposterior lesion are summarized in table 2. Cases 1 to 7 inclusive were illustrative of this group. In cases 8, 9 and 10 a minor variation was evident in that the signs of the anterior lesion did not appear in the limb leads. This was to be expected because a certain number of infarcts of the anterior wall fail to give evidence of their presence in limb leads.⁴

The chief electrocardiographic characteristics of the cases in which both limb and chest leads show evidence of acute anterior and posterior infarction may be summed up as follows:

1. Lead II usually shows a higher deviation of the RS-T interval than leads I or III. This might be expected for the following reasons:
A. The RS-T interval in lead I tends to be elevated in anterior infarction and slightly depressed or iso-electric in posterior infarction. In anteroposterior infarction these deviations tend to neutralize each other; consequently the RS-T interval in lead I is usually elevated, but less so than in uncomplicated anterior infarction. *B.* The RS-T interval in lead III tends to be elevated in posterior infarction and slightly depressed or iso-electric in anterior infarction. In anteroposterior infarction these deviations tend to neutralize one another. Consequently the RS-T

4. (a) Wood, Bellet, McMillan and Wolferth.² (b) Wood, F. C., and Wolferth, C. C.: Huge T Waves in Precordial Leads in Cardiac Infarction, *Am. Heart J.* 9:706 (Aug.) 1934. (c) We have seen one other case,^{4b} not included in table 1, in which there was evidence of a lesion in the posterior wall in the limb leads. Lead IV showed a huge upright T wave which we believe to be a sign of a lesion in the anterior wall.

TABLE 1.—*Electrocardiographic Evidence Suggesting Acute Infarction of Both Walls of the Left Ventricle in Ten Cases*

Case and Date of Attack	Deviation of RS-T Interval, Mm.						Q Wave in Lead III	Initial Downward Deflection in Leads IV and V	Electrocardiographic Localization	Necropsy	Comment
	I	II	III	IV	V	VI					
1. J. L. 12/12/33	+1	+2	+0.5	-6	-4	+1.5	Very small	Absent	Both chest and limb leads showed main lesion anterior; bundle septal lesion	Confirmed electro-graphic localization	Died 12/26/33 (case 1, fig. 1)
2. H. F. 10/28/33	+1	+2	+1	-3	-1	+1.5			Both chest and limb leads showed anterior and posterior lesion; main lesion posterior	Confirmed electro-cardiographic localization	Died 3/6/34 (case 2, fig. 2A)
3. S. C. 11/26/33	+1	+2.5	+1.5	-6	-4	+2	Significant type	Small at first in lead IV; later became normal	Both chest and limb leads showed anterior and posterior lesion; lesion equally suggested	0	Died 12/12/33
4. D. F. 3/15/32	+0.5	+1.5	+1	-4	-3	+1	Significant type	Absent	Both chest and limb leads showed anterior and posterior lesion; main lesion anterior	0	
5. A. D. 2/6/34	+1	+3	+2	-5	-3	+2	Questionable	Absent	Both chest and limb leads showed anterior and posterior lesion; main lesion anterior	0	
6. H. S. 1/19/33	+2	+3	+1	-4	-1	+2.5	Absent	Present	Both chest and limb leads showed anterior and posterior lesion; main lesion anterior	0	
7. M. F. 7/27/33	+0.5	+2	+1.5	-2	0	+2	Small		Both chest and limb leads showed anterior and posterior lesion; on 1/20 signs were purely posterior; signs of old posterior lesion after healing, main lesion probably posterior	0	Recovered; last heard from on 3/20/34*
8. A. S. 12/7/33	0	+2	+2	-3	0	+2	Significant type	Absent (re-turned later)	Both chest and limb leads showed anterior and posterior lesion; main lesion probably posterior	0	Recovered; last seen on 7/13/34; condition fair; (fig. 3)
9. A. S. 2/23/34	-2.5	+2	+4	-4	-1	+3	Absent	Small throughout	Limb leads showed posterior lesion only; chest leads showed both anterior and posterior lesion; main lesion probably posterior	0	Discharged 3/24/33; last seen 4/2/34; moderate restriction of activity due to angina on effort
10. G. H. 1/27/34	0	+1.5	+1.5	-1	0	+1	Significant type	Absent	Limb leads showed posterior lesion only; chest leads showed both anterior and posterior lesion; lesion equally suggested	0	Died 9/24/33; had several previous attacks suggesting coronary occlusion
T-1 = -4. T-4 = +7 on 2/8/34											3/14/33 incomplete heart block developed; died 5/4/34
* Wood, Bellet, McMillan and Wolferth, ² case 18, chart 6.											Previous attacks 11/8/33 and 2/1/34; died of cardiac failure 5/2/34
											Previous attack 1/7/34; 3/10/34 in fairly good condition

interval in lead III is usually elevated, but less so than in uncomplicated posterior infarction. C. The elevation of the RS-T interval in lead II, the algebraic sum of the elevations in leads I and III, is greater than it is in either lead I or lead III. This is a finding which we have not observed in uncomplicated anterior or posterior infarction. 2. Lead V usually shows less deviation of the RS-T interval than lead IV. Anterior infarction causes a depression of the RS-T interval in lead IV. Posterior infarction usually causes an elevation of the RS-T interval in lead VI. Therefore, the RS-T interval in lead V, the algebraic sum of the elevations in leads IV and VI, shows less deviation than in lead IV. These phenomena of the RS-T interval we believe are the most reliable signs of acute anteroposterior infarction.

TABLE 2.—*Deviations of the RS-T Interval in Acute Cardiac Infarction*

	Anterior	Posterior	Anteroposterior
Lead I	Upward (tend to be largest of the limb leads)	Downward	Tend to be slightly upward
Lead II	Usually none (always less than in lead I)	Upward (always less than in lead III)	Upward (larger than in lead I or lead III)
Lead III	Downward, if any	Upward (tend to be largest of the limb leads)	Tend to be slightly upward
Lead IV	Downward	Often none (upward, if any)	Downward
Lead V	Downward (about equal to those in lead IV)	Upward (tend to be larger than those in lead IV)	Usually downward, but less than in lead IV
Lead VI	Usually none, or slightly downward	Upward	Tend to be slightly upward

The changes in the QRS complex are sometimes helpful. The disappearance of the initial downward deflection in lead IV indicates an anterior lesion; the development of a deep Q wave in lead III following an attack usually indicates a lesion in the posterior wall. When both these signs are present the probability of lesions in both surfaces must be considered (case 11). However, in the absence of the characteristic deviations of the RS-T interval, one cannot tell whether the lesions which produced the changes in the QRS complex are acute or old since these changes tend to persist after healing.

The presence of the typical electrocardiographic signs of acute anteroposterior infarction, outlined in table 2, is probably fairly reliable evidence of the existence of this lesion. On the other hand, the absence of these signs cannot be regarded as certain evidence that such a lesion does not exist. For example, in case 1 the signs of the acute anteroposterior lesion which were present on December 15 were absent on December 21. Only the signs of an anterior lesion remained. In case 11 an electrocardiogram (fig. 2 B) taken five days (or more) after the

onset clearly showed the lesion in the anterior wall, but the signs of the lesion in the posterior wall were doubtful. As healing takes place the major lesion tends to dominate the electrocardiographic picture. The signs of the minor lesion may disappear after a few days.

Case 11 was one of acute anteroposterior infarction proved by necropsy in which the electrocardiographic findings were suggestive but not conclusive.

CASE 11.—F. N. was a Negro woman of 43 with diabetes mellitus. She was admitted on Jan. 26, 1934, to the Philadelphia General Hospital in the service of Dr. Dillon, in diabetic coma. Her husband stated that she had complained of pain in the lower sternal region for about a week prior to admission to the hospital. On January 22 the pain became so severe that she was forced to go to bed. Dyspnea and weakness increased. On the day of admission to the hospital she grew comatose.

Physical examination revealed Kussmaul's breathing, coma and an odor of acetone on the breath. The temperature was 102 F.; the pulse rate was 120, and the respiratory rate was 30. The blood pressure was 90 systolic and 60 diastolic. A loud systolic murmur was heard at the apex. No other abnormalities were noted. The value for blood sugar was 592 mg. per hundred cubic centimeters. The carbon dioxide content of the blood was 19 mg. The leukocyte count was 24,000. The diabetic coma responded satisfactorily to treatment. The acidosis was controlled. Death occurred suddenly on January 28 at 8:55 p. m.

Necropsy was performed by Dr. McCutcheon on January 29. The left anterior descending artery was occluded by a recent thrombus 1 cm. from its origin. The circumflex branch was sclerosed but patent. The lumen of the right coronary artery was narrowed at several points, but never completely occluded. There was an acute infarct involving the lower half of the anterior surface of the left ventricle, the lower half of the ventricular septum and the lower quarter of the posterior surface of the left ventricle. Mural thrombi were adherent to the inner surface of the infarcted area. The ventricular wall near the apex was extremely thin. The ventricular septum bulged toward the right ventricle.

Only one electrocardiographic tracing was taken, on January 27 (fig. 2 B). Lead I showed a slight elevation of the RS-T interval. In leads II and III it was difficult to be sure where the RS-T interval began, but there seemed to be a slightly high take off in lead II. Leads IV and V showed the typical signs of an acute anterior infarct. Lead VI showed a slightly high take off of the RS-T interval. A deep Q wave was seen in leads III and VI.

Summary.—A case was reported of coronary occlusion with involvement of both anterior and posterior surfaces of the left ventricle. Electrocardiographic evidences of acute infarction of the anterior wall were present. The deep Q wave in lead III and the slightly high take off in leads II and VI suggested the possibility of a lesion of the posterior wall as well.

COMMENT

The only data we possess which serve to indicate the incidence of acute anteroposterior infarction are supplied by the following figures: In 10 of our series of 104 cases of acute coronary occlusion adequately

ACTION OF OIL OF PEPPERMINT ON THE SECRETION AND MOTILITY OF THE STOMACH IN MAN

JACOB MEYER, M.D.

LOUIS SCHEMAN, M.D.

AND

H. NECHELES, M.D., PH.D.

CHICAGO

While conducting experiments on the mechanism of pain in peptic ulcer it occurred to one of us to try the effect of essential oils. Oil of peppermint was selected because it is known as a household remedy for relieving gastric distress. This paper is a report of the action of oil of peppermint on the motility and secretion of the stomach of patients with peptic ulcer.

The "Pentsao Kang Mu" (Li Shih Chen, 1597 A. D.),¹ in which is summarized the oldest knowledge of Chinese medicine, records the use of oil of peppermint as an antispasmodic. According to Heupke,² peppermint as a remedy was mentioned at the time of Charlemagne.

Wallace and Jackson³ found that oil of peppermint in the intestine influences gastric secretion by reflex action. Meyer and Gottlieb in their textbook⁴ stated that carminatives increase the muscular activity of the alimentary canal. Muirhead and Gerald⁵ found that a small amount of a volatile oil increases the motility of isolated segments of intestine and that a larger dose decreases it. Cushny⁶ stated that volatile oils relax the musculature of the stomach and intestine. Gunn⁷ likewise reported that carminative volatile oils depress

From the Department of Gastro-Intestinal Physiology and the Stomach Study Group, Nelson Morris Institute of the Michael Reese Hospital.

The study was carried on by the aid of a grant from the Louis L. Cohn and Kuppenheimer Funds to the Stomach Group of the Michael Reese Hospital.

1. Stuart, G. A.: Chinese Materia Medica, Shanghai, China, American Presbyterian Press, 1911.

2. Heupke, W., and Hollaender, E.: *Deutsches Arch. f. klin. Med.* **173**:241, 1932.

3. Wallace, G. B., and Jackson, H. C.: *Am. J. Physiol.* **8**:xvii, 1903.

4. Meyer, H. H., and Gottlieb, R.: *Pharmacology*, translated by J. Taylor Halsey, Philadelphia, J. B. Lippincott Company, 1915, p. 211.

5. Muirhead, A. L., and Gerald, F. G.: *J. Pharmacol. & Exper. Therap.* **8**: 253, 1916.

6. Cushny, A. R.: *Textbook of Pharmacology and Therapeutics*, ed. 7, Philadelphia, Lea & Febiger, 1918, p. 63.

7. Gunn, J. W. C.: *J. Pharmacol. & Exper. Therap.* **16**:39, 1920.

0.9 per cent saline solution was washed into the stomach through the tube. While in some tests there was a small change in acidity after the oil of peppermint was given, in the majority a considerable reduction of free acid occurred, which is represented in chart 1 by the mean curve. In table 1 the results shown in chart 1 are expressed as percentage of change. The average of the control values is compared with the lowest points of the curves after the oil of peppermint was given. The average decrease thus was 65 per cent. Control tests with 10 cc. of 0.9 per cent saline solution only showed no influence on the free acidity.

Although these results appear to prove a strong depressing action of oil of peppermint on the secretion of free acid by the stomach, more conclusive proof was demanded. The variations of acidity in the stomach of a normal person and of a patient with peptic ulcer may be considerable, and although it is improbable that the variations should work one way only, we wanted better proof. A sufficiently strong secretagogue stimulus was applied to the stomach, first alone, and then with oil of peppermint. Injection of 100 cc. of a 7 per cent solution of ethyl alcohol through the stomach tube and the subcutaneous injection of 0.35 mg. of

TABLE 1.—*Action of Oil of Peppermint (from 1 to 2 cc.) on the Free Acidity of the Stomach After Fasting*

Patient	Free Acid in Clinical Degrees		
	Before	After	± Percentage of Change
1.....	118	80	—25
2.....	80	80	0
3.....	76	50	—33
4.....	39	0	—100
	60	15	—75
5.....	45	25	—44
	40	25	—38
6.....	68	0	—100
7.....	38	0	—100
8.....	29	0	—100
9.....	16	0	—100
Average decrease of acidity.....			—65

histamine acid phosphate were used.¹⁴ The tests with the secretagogue alone and with oil of peppermint were carried out, of course, on two different days, but in all except two patients they were made within the same week. The areas of both curves for the first two hours after the application of the stimulus were measured with a planimeter and the difference between them expressed as percentage of change.

Eighteen tests were performed on seventeen patients with peptic ulcer. Chart 2 represents the results in a typical case in which complete suppression of free acidity resulted in a patient with peptic ulcer of the duodenum. Alcohol alone produces a good response of free acid, and the same is true for alcohol plus olive oil, while the administration of alcohol plus oil of peppermint is not followed by the secretion of free acid. The combined acid does not show an increase which might explain the disappearance of the free acid; this was true for most of the other tests. The volume of secretion was not changed markedly in this test, although in other tests it was increased. We are aware that comparison of the two areas of secretion involves a great difficulty. The same person has rarely the same degree of free acidity in his stomach at rest. Since the tests were performed

14. Seidmon, E. E., and Necheles, H.: Illinois M. J. 67:458, 1935.

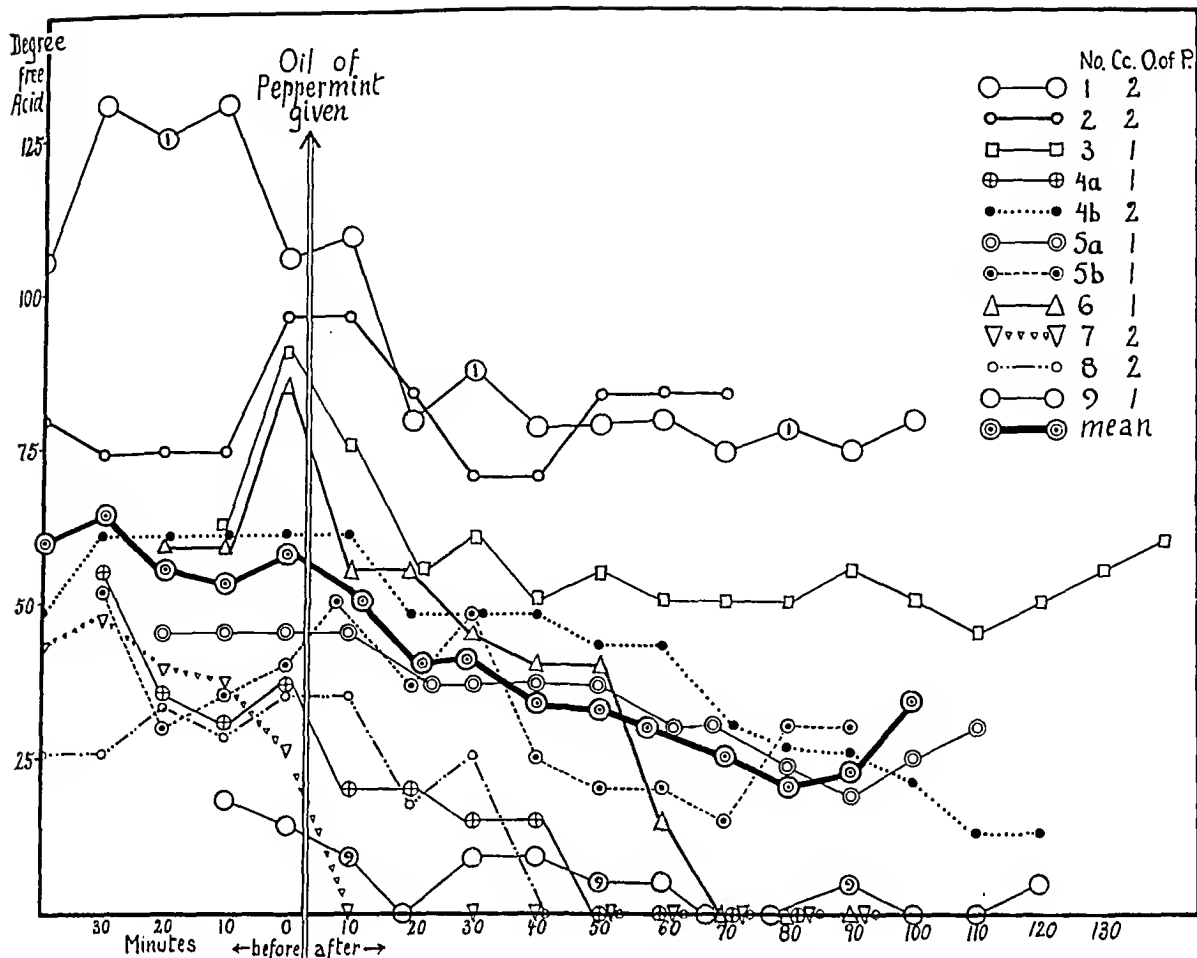


Fig. 1.—The action of oil of peppermint on the gastric secretion of the stomachs of patients with peptic ulcer after fasting.

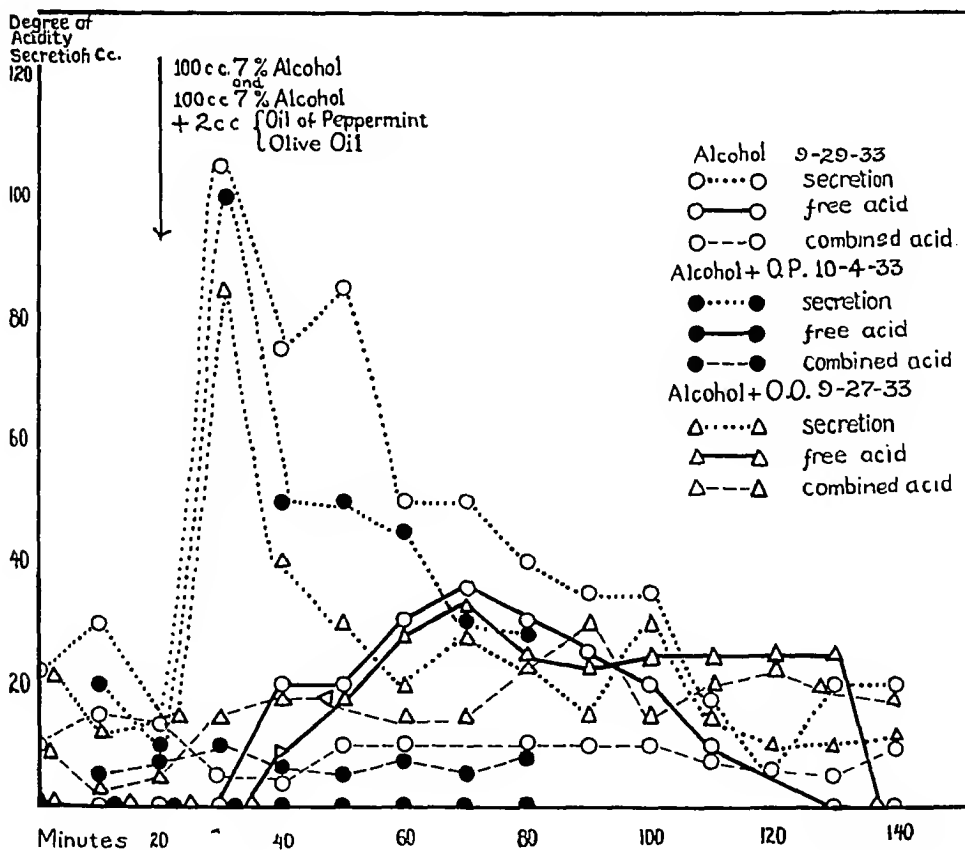


Fig. 2.—Typical results in one patient of a series of tests with alcohol, alcohol and oil of peppermint and alcohol and olive oil.

on two different days, the secretory impulses of the stomach at rest may have been different on the two days, and the action of the oil of peppermint might have been stronger on the day on which the control test was carried out than on the day when the test with oil of peppermint was carried out and vice versa. We therefore have noted the degree of free acid of the stomach after fasting in table 2, both before the alcohol, and before the alcohol and oil of peppermint, were administered.

TABLE 2.—*Results of Tests with Alcohol and with Alcohol and Oil of Peppermint on Patients with Peptic Ulcer**

No.	Degree of Free Acid in Stomach after Fasting		Percentage of Change in Area after Oil of Peppermint	
	Alcohol	Alcohol-Oil of Peppermint	Free Acid	Secretion
1....	98	125	— 46	— 5
2...	18	50	— 43	+ 69
3..	71	83	— 0.3	+ 2
4...	83	111	— 10	+ 32
5....	35	23	— 60	— 68
6..	10	39	+ 19	+ 84
7...	49	23	— 51	— 28
8..	63	88	— 43	+113
9..	131	25	— 46	+110
10..	15	7	—100	+212
11....	0	3	—100	— 19
12...	33	5	— 71	+ 11
13..	35	0	— 56	— 26
14....	41	51	— 4	— 9
15....	0	5	— 47	— 47
16....	0	18	+ 25	— 47
17... ..	30	33	— 43	— 25
	30	35	— 43	+ 17

* The control trials and tests were made within one week except in cases 8 and 10 in which there was an interval of six and eight weeks, respectively.

TABLE 3.—*Comparison of the Free Acidity Before Administration of Alcohol and that Before Administration of Alcohol and Oil of Peppermint*

	Free Acidity Higher in Alcohol Controls	Free Acidity Higher in Alcohol and Oil of Peppermint Controls	Free Acidity the Same in Alcohol and in Alcohol and Oil of Peppermint Controls
Number of times.....	5	7	6
Percentage of change of area of free acidity after alcohol and oil of peppermint ..	—57	—13	—56
Percentage of change of area of secretion after alcohol and oil of peppermint ..	— 1	+35	+22

The depressing effect of oil of peppermint on gastric free acidity was of greater or less significance as the levels for acid after fasting were higher or lower before the administration of alcohol and oil of peppermint than before the administration of alcohol in the control tests.

In table 3 we have grouped the results noted in table 2 accordingly. The most important result was that noted for the group in which the free acidity of the controls of the tests with alcohol and those with alcohol and oil of peppermint were the same, the average decrease in free acidity after the administration of alcohol and oil of peppermint being 56 per cent. In the tests in which the levels of acid after fasting following the alcohol tests were higher, the average decrease

of free acidity was 57 per cent. In those tests in which the acidity of the controls before alcohol and oil of peppermint were given was higher there was a decrease of free acidity of only 13 per cent after alcohol and oil of peppermint were given. These results indicate that there is a clearcut diminution of secretion of acid after alcohol and oil of peppermint are given. There was some increase in the volume of secretion after the administration of alcohol and oil of peppermint.

Histamine is a more powerful gastric secretagogue than alcohol. Simultaneously with the subcutaneous injection of 0.35 mg. of histamine acid phosphate, 2 cc. of oil of peppermint was given through the Rehfuess tube. Except in case 2, in

TABLE 4.—*Results of Tests with Histamine and Histamine and Oil of Peppermint on Patients with Peptic Ulcer*

No.	Degree of Free Acid in the Stomach after Fasting		Percentage of Change in Area after Oil of Peppermint		Interval Between Tests with Histamine and Histamine-Oil of Peppermint, Weeks
	With Histamine	With Histamine and Oil of Peppermint	Free Acid	Secretion	
1	103	61	—51	+ 14	1
2†	25	46	+78	+100	2½
3	14	29	—46	— 20	2½
4	65	54	—24	+ 64	1
5	80	64	—23	— 36	8

* Histamine acid phosphate was given subcutaneously in doses of 0.35 mg. (except in case 3 in which 0.5 mg. was given) and 2 cc. of oil of peppermint was given with 10 cc. of physiologic solution of sodium chloride.

† This patient had hyperthyroid disturbance.

TABLE 5.—*Results of Tests with Alcohol and Alcohol and Olive Oil on Patients with Peptic Ulcer*

Case	Percentage of Change in Area of Secretion of Free Acid	
	After Alcohol and Olive Oil	After Alcohol and Oil of Peppermint
1.....	—16	—100
2.....	+27	— 71
3.....	—17	— 56
4.....	+16	+ 4
5.....	+95	+ 25
6.....	—14	— 43
Average.....	+16	— 40

which a hyperthyroid condition existed, there was a diminution of secretion of acid in all tests after oil of peppermint was given, even if higher acid levels are accounted for in the controls for the histamine tests (table 4). Since we consider histamine to be so much more powerful a secretagogue than 7 per cent alcohol we expected to find a smaller reduction after alcohol and oil of peppermint than after histamine and oil of peppermint were administered.

In trying to analyze the depressant action of oil of peppermint we made some control experiments on patients on whom tests with alcohol and oil of peppermint had been carried out previously. Olive oil was used in amounts of 2 cc. to exclude the possibility of inhibition of the secretion of acid by oil. In table 5 it is demonstrated that there was no diminution of free acidity similar to that observed after alcohol and oil of peppermint were given. All tests were done within ten days after the control tests were carried out.

Further tests were made in order to find out whether the oil of peppermint would depress the secretion of gastric acid when given thirty minutes after the alcohol or histamine was administered. Four such tests were carried out, and no significant depressing action was demonstrated. Negative results were obtained when menthol (0.5 Gm. in 100 cc. of 7 per cent alcohol), one of the main constituents of oil of peppermint, was given two patients. Phenol (0.1 Gm. in 100 cc. of 7 per cent alcohol) was given once and had a depressant action only slightly lower than that of oil of peppermint.

In one patient in whom there was a good acid secretory response to 100 cc. of 7 per cent alcohol and a complete suppression of free acid after 100 cc. of 7 per cent alcohol plus 2 cc. of oil of peppermint the secretion of mucus was measured. It was thought that increased secretion of gastric mucus after oil of peppermint was given might be responsible for the decrease of the free acidity. The visible mucus was measured by centrifugating every ten minute sample of stomach juice in graduate tubes. Instead of aspirating every sample at the end of each ten minute period continuous suction was used.¹⁵

As shown in chart 3, there was no increase of secretion of mucus after alcohol and oil of peppermint were given. (The control values for the secretion of mucus

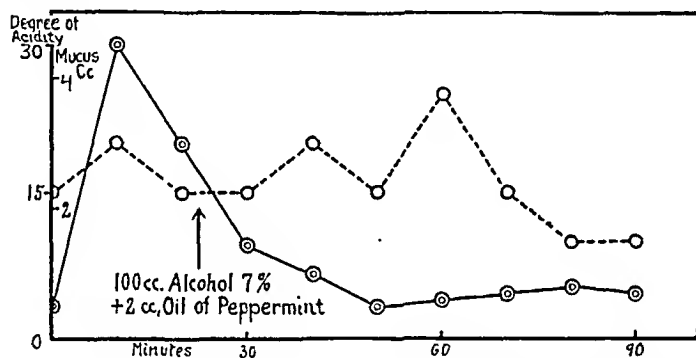


Fig. 3.—The secretion of gastric mucus (unbroken line) and combined acid (broken line) after the administration of 100 cc. of 7 per cent alcohol and 2 cc. of oil of peppermint.

of the resting stomach are always relatively high.) Thus, oil of peppermint does not increase the secretion of visible mucus which might neutralize the free acid and raise the values of the combined acid. No determinations of dissolved mucus were made.

Gastric Motility After Oil of Peppermint Was Given.—Since oil of peppermint might hasten the emptying time of the stomach, patients and dogs were used to investigate this question. The usual balloon method of Carlson and Luckhardt¹⁶ was employed. Through a stomach tube in the patients and through a gastric fistula in the dogs, oil of peppermint was passed after a sufficient period of control. The oil of peppermint was given by constant slow drip or in amounts of from 2 to 4 cc. over a period of time. The experiments lasted from two to six hours.

15. Necheles, H., and Coyne, A.: Secretion of Mucus and Acid by the Stomach in Healthy Persons and in Persons with Peptic Ulcer, *Arch. Int. Med.* 55:395 (March) 1935.

16. Carlson, A. J.: *The Control of Hunger in Health and Disease*, Chicago, University of Chicago Press, 1919.

Each kymographic record was divided into twenty minute periods, and the type and height of the contractions¹⁶ of the stomach were tabulated (table 6). As seen in table 6, there was a depression of motility only when large, unphysiologic amounts of oil of peppermint were given. Only once was there a distinct depression of motility in the dog with a relatively small amount of oil of peppermint. These results are somewhat in contradiction to recent experiments carried on in this laboratory and in the roentgen department of Michael Reese Hospital. Normal persons show a considerable decrease in the emptying time of the stomach after a barium sulphate meal plus 2 cc. of oil of peppermint. These results and those obtained by means of the balloon technic will be discussed in another paper.¹⁷

Experiments on Dogs.—A great number of tests were performed on dogs with stomach pouches (Pavlov and Heidenhain). It could be demonstrated that the secretory action of small amounts of histamine given subcutaneously could be diminished or suppressed completely when simultaneously with the injection of the histamine the pouch was filled with oil of peppermint for five minutes. Oil of peppermint when put into the main portion of the stomach does not have the same effect on the secretion of the pouch. These results will be reported later.¹⁸

TABLE 6.—*The Action of Oil of Peppermint on Gastric Motility Tested by Means of a Balloon in the Stomach**

Doses of Oil of Peppermint	Number of Tests	
	Depression of Motility	No Change of Motility
Above 10 cc. in patients; above 4 cc. in dog.....	6	2
Below 10 cc. in patients; below 4 cc. in dog.....	1	11

* Fifteen tests were carried out on thirteen patients with peptic ulcer and five tests on one dog with a gastrostomy.

COMMENT

Oil of peppermint when given by itself or with a secretory stimulant depresses the secretion of acid by the stomach. The mechanism of the depressing action of oil of peppermint on gastric acidity has not been explained to our satisfaction. The rôle of the chlorides was considered as a possible factor. A number of determinations of the chloride content have been made on samples of gastric juice before and after the introduction of alcohol and of alcohol and oil of peppermint into the stomach. The level of the chlorides was not affected when the free and combined acidity decreased after alcohol and oil of peppermint were given. This may be indicative of a change in the mechanism of secretion, i. e., suppression of the free hydrochloric acid and possible increase of the sodium chloride.

17. Sapoznik, H. I.; Arens, R. A.; Meyer, Jacob, and Necheles, H.: The Effect of Oil of Peppermint on the Emptying Time of the Stomach, *J. A. M. A.* **104**:1792 (May 18) 1935.

18. Necheles, H., and Meyer, Jacob: *Am. J. Physiol.* **110**:686, 1935.

Oil of peppermint is a mixture of a number of substances,¹⁹ and further analysis of the action of its components is necessary. One of its most characteristic constituents, menthol, was found to have no acid-depressing effects. The oily constituents certainly are not enough in quantity in 2 cc. amounts of oil of peppermint to exhibit the typical depressant action of oil on gastric secretion, and, besides, this has been found in a number of control tests with olive oil. The experiments on dogs with gastric pouches indicate that the action of the oil is probably a local one on the mucosa of the pouch.

If one accepts the evidence given by Heinz¹³ that oil of peppermint increases the secretion of bile, this fact helps to explain the popular belief in the favorable action of oil of peppermint in relieving distress caused by gastric hyperacidity. The acid that is still secreted by the stomach is more readily neutralized by the increased volume of bile meeting it in the duodenum. Of course, one must consider here the time relations, i. e., the question of how soon more bile is emptied into the duodenum after the injection of oil of peppermint and how much faster the stomach actually empties itself.

A number of patients with peptic ulcer are now being treated in our clinic with the essence of oil of peppermint. In a few, relief of pain has definitely been noted but the period of observation is not sufficient to warrant a statement. In view of the popular use of peppermint for relief of gastric distress and the interest and importance of the mechanism of pain in ulcer it might readily be argued by those who favor the theory of acid in relation to pain that the relief of symptoms following the use of oil of peppermint is due to a diminution in free acid. However, there is still considerable dispute as to the factors involved in pain in peptic ulcer.²⁰ In a previous article one of us proved that relief of pain occurred independent of the degree of free acidity in patients with chronic peptic ulcer. It was suggested that the relief of symptoms in patients with peptic ulcer following the use of foreign protein was due to an improvement of the circulation in the vascular bed in and about the ulcerated area, and the hypothesis was advanced that the pain of ulcer is due to ischemia and asphyxia resulting from depletion of the vascular bed in and about the ulcerated area.²¹ It was on the basis of this conception of the mechanism of pain in peptic ulcer that it occurred to one of us to try the effects of an essential oil, a substance which might

19. Kremers, R. E.: *J. Biol. Chem.* **50**:31, 1922.

20. Hurst, A. F.: *The Goulstonian Lectures on the Sensibility of the Alimentary Canal*, New York, Oxford University Press, 1911. Carlson, A. J.: *Am. J. Physiol.* **45**:81, 1917. Ivy, A. C.: *Contributions to the Physiology of the Stomach: Studies on Gastric Ulcer*, *Arch. Int. Med.* **25**:6 (Jan.) 1920.

21. Meyer, Jacob, and Kartoon, L. B.: *The Effect of Intravenous Injections of Foreign Protein on Peptic Ulcer*, *Arch. Int. Med.* **46**:768 (Nov.) 1930.

cause a local hyperemia. The sense of warmth and feeling of ease following the ingestion of essence of oil of peppermint is well known. While we hope to report further on the mechanism of pain, the present study has been directed to an investigation of gastric secretion and motility following the administration of oil of peppermint.

SUMMARY

In patients suffering from peptic ulcer the secretion of acid of the stomach at rest (basal secretion) is depressed or inhibited by oil of peppermint. While the secretion of acid by the stomach of patients with peptic ulcer was abundant after alcohol and histamine were given in control tests, it was completely abolished in some instances and considerably diminished in most instances after simultaneous administration of oil of peppermint. This depression was probably due not to the neutralizing effect of visible mucus but to a local effect on the mucosa and to a shortening of the emptying time of the stomach.

ACUTE CARBON TETRACHLORIDE POISONING

REPORT OF A CASE

EARL R. LEHNHERR, M.D.

BOSTON

The dangers of carbon tetrachloride and its popularity in commercial preparations have been stressed recently.¹ Many cases of industrial and accidental poisoning have been reported,² but laboratory data on actual cases comparable to those available from experimental studies on animals is still lacking.³ The case reported here is presented to illustrate the important changes in the plasma lipids observed in a case of severe damage to the liver.

REPORT OF A CASE

History.—An unemployed white man 38 years old, for eight years accustomed to drink about 2 pints (946.3 cc.) of ethyl alcohol once or twice weekly, was admitted to the Boston City Hospital eight hours after drinking 4 or 5 ounces (118 to 148 cc.) of pure carbon tetrachloride mistaken for ethyl alcohol.

There was no untoward reaction for three hours; then vomiting occurred immediately after eating, followed by intermittent periods of mental cloudiness and confusion. A physician who was called gave the patient gastric lavage, administered sodium bicarbonate and solutions of egg white and advised immediate hospitalization.

One hour before admittance the patient had severe colicky abdominal pains with numerous watery stools accompanied by large amounts of flatus and tenesmus.

Physical Examination.—Examination revealed a well developed and well nourished man who was obviously ill. The breath had a definite odor of carbon tetrachloride. The skin was pale, cold and slightly cyanotic. The tongue was coated. The heart was slightly enlarged. The sounds were regular and of fair quality. There were a short systolic murmur at the apex and a soft diastolic murmur heard best over the area of the mitral valve. The second aortic sound was louder than

From the Laboratory for Surgical Research of the Boston City Hospital.

1. Volatile Poisons in the American Home, editorial, J. A. M. A. **101**:1238 (Oct. 14) 1933.

2. McMahon, H. E., and Weiss, S.: Carbon Tetrachloride Poisoning with Macroscopic Fat in the Pulmonary Artery, Am. J. Path. **5**:623 (Nov.) 1929. Butsch, W. L.: Cirrhosis of the Liver Caused by Carbon Tetrachloride, J. A. M. A. **99**:728 (Aug. 27) 1932. Poisoning from Carbon Tetrachloride, foreign letter (Paris), *ibid.* **99**:1276 (Oct. 8) 1932. McGuire, L. W.: Carbon Tetrachloride Poisoning, *ibid.* **99**:988 (Sept. 17) 1932.

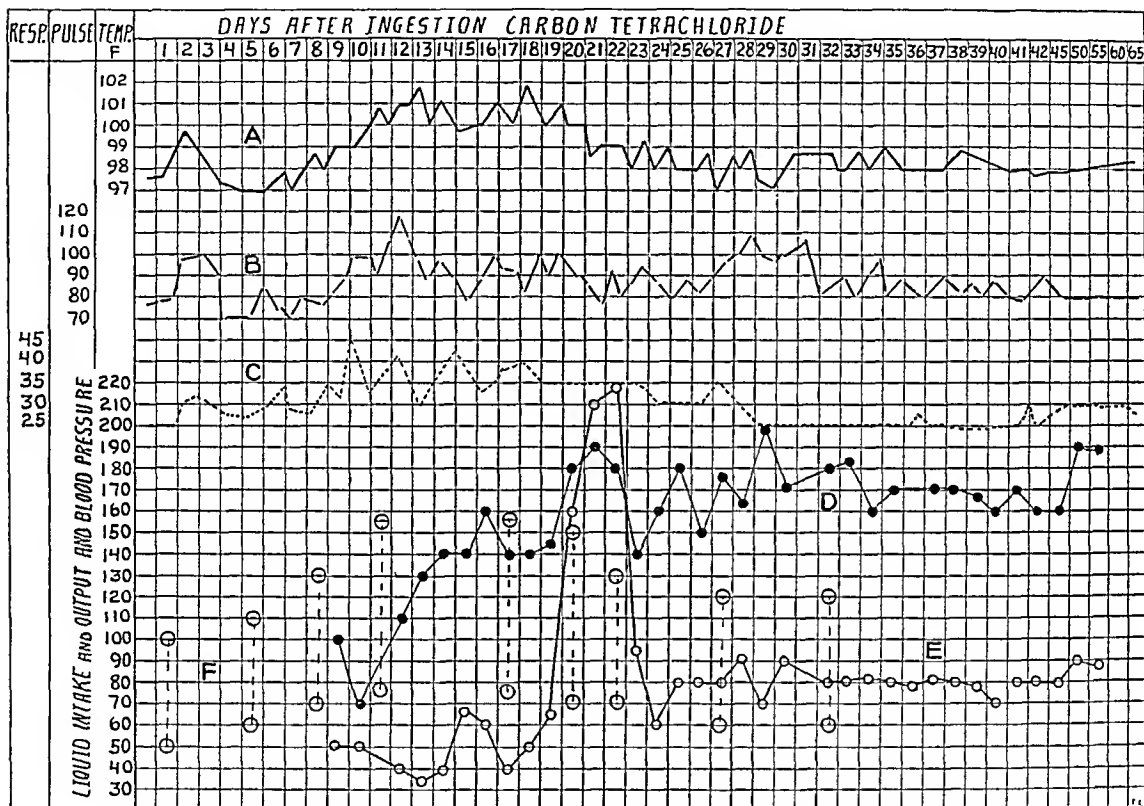
3. Lamson, P. A., et al.: The Pharmacology and Toxicology of Carbon Tetrachloride, J. Pharmacol. & Exper. Therap. **22**:215 (Nov.) 1923.

Laboratory Data and Parenteral Medication in a Case of Carbon Tetrachloride Poisoning

Days After Ingestion of Poison	Plasma Lipids, Mg. per 100 Cc.					Chemical Analysis of Blood, Mg. per 100 Cc.										Studies of the Blood				Urinalysis				Parenteral Medication		
	Cholesterol			Total Fatty Acids		Total Lipid	Icteric Index	Bilirubin, Mg. per 100 Cc.	Nonprotein Nitrogen				Hemoglobin (Sahlb), per Cent	Red Cells*	White Cells*	Specific Gravity	Albumin	Red Cellst	White Cellst	Castst	Hypodermoclysis,† Cc.	50% Dextrose, Cc.	Calcium Gluconate, Gm.			
	Total	Free	Ester	Total	Urea				Amino Acid	Uric Acid	Creatinine	Sugar														
1	74	45	29	218	86	292	55	3.5	135	146	6.3	13.0	7.2	99	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
2	78	54	32	277	86	355	45	2.5	132	116	5.9	11.5	7.6	94	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
3	86	64	32	338	106	424	50	2.5	132	116	5.9	11.5	7.6	94	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
4	89	22	67	268	111	357	65	2.3	136	95	7.1	11.0	4.0	112	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
5	81	36	45	370	108	451	25	2.5	123	95	5.8	10.4	6.1	110	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
6	95	17	78	254	118	349	45	2.0	118	73	5.1	9.0	4.5	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
7	86	37	49	271	167	357	18	1.8	119	73	5.1	9.0	4.5	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
8	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
9	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
10	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
11	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
12	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
13	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
14	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
15	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
16	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
17	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
18	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
19	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
20	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
21	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
22	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
23	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
24	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
25	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
26	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
27	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
28	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
29	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
30	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
31	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
32	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
33	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
34	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
35	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
36	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
37	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
38	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
39	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
40	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
41	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
42	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
43	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
44	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
45	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
46	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
47	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
48	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
49	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
50	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
51	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
52	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
53	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
54	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
55	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560	9.1	4.1	5.8	0	0	0	1,250	125	0.8	
56	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	122	91	5,560										

the second pulmonic sound. The arterial blood pressure was 105 millimeters of mercury systolic and 50 mm. diastolic. The lungs were clear. The abdomen was not distended, but there were generalized muscular spasm, resistance and tenderness on palpation. No mass was felt. There was no evidence of ascites. The extremities were normal. All the reflexes were hyperactive.

Treatment and Clinical Course.—A therapeutic regimen intended to combat damage to the liver was instituted. This consisted of a diet high in carbohydrate (200 Gm. daily), daily intravenous injections of dextrose and calcium gluconate (table), oral administration of 1.8 Gm. of calcium lactate daily and rectal administration of a solution of dextrose (120 cc. of a 10 per cent solution every four hours).



A record of the temperature (A), pulse rate (B), respiratory rate (C), fluid intake (ounces), (D), fluid output (ounces), (E) and systolic and diastolic blood pressure (millimeters of mercury) (F) in a case of acute carbon tetrachloride poisoning.

The patient complained of severe abdominal cramps and generalized aches and pains in the muscles, and was unable to retain fluids given by mouth during the first three days. The watery stools passed frequently during the first thirty-six hours had an unmistakable odor of carbon tetrachloride. On the third day the sclerae showed definite evidence of jaundice. On the sixth day the patient became dyspneic and had a dry, hacking cough. The sputum was watery and contained many red cells. On the tenth day there was pitting edema of the ankles, sacrum and scrotum. Shifting dullness was demonstrated in the abdomen at this time. The lungs contained many râles, which were most marked at the bases and in

the midanterior regions. The temperature rose to 102 F. and remained elevated until the twenty-first day (chart).

Roentgenograms of the chest at this time showed bilateral consolidation of the lungs similar to that seen in cases of bronchopneumonia (roentgen studies of the chest are given later). The patient was dangerously ill during the first three weeks.

Eighteen grains (1.17 Gm.) of digitalis was given during the thirteenth and fourteenth days. Administration of digitalis was continued in a daily dose of $1\frac{1}{2}$ grains (0.097 Gm.) through the twenty-sixth day when it was omitted until the fiftieth day. The patient then received 3 grains (0.195 Gm.) daily for seven days.

Improvement was rapid after the twenty-first day. There was temporary diuresis (chart) with the disappearance of the ascites and edema. The patient was symptom-free in five weeks and remained so until his discharge from the hospital on the sixty-fifth day after drinking the poison.

The chart shows the temperature, pulse rate, respiratory rate, fluid intake, urinary output and systolic and diastolic arterial blood pressure. The laboratory data are given in the table.

Roentgen Studies of the Chest.—On the fourteenth day there was a diffuse bilateral mottling similar to that seen in cases of bronchopneumonia or advanced tuberculosis. This picture was interpreted as possibly being due to multiple fat emboli in the lungs. On the sixteenth day there was irregular density throughout both pulmonary fields which was most marked in the upper third and about the hili. The density was interpreted as being due to a consolidation of the parenchyma. On the twenty-sixth day there was less consolidation than was seen in the previous picture. The consolidation was still present in the upper third of the right side, and the picture was consistent with that of bronchopneumonia in the convalescent stage. On the thirty-sixth day the lungs were clear except for a faint cloudiness at the base of the right lung. On the fiftieth day and on the sixty-second day the chest appeared normal.

Electrocardiograms.—On the eleventh day there was evidence of sino-auricular tachycardia with a rate of 103 and a PR interval of 0.14 second. There were high P_2 and P_3 waves. The QRS interval was 0.09 second. The T wave was upright in all leads; the T_2 wave was high. The axis was normal. On the fiftieth day there was normal sinus rhythm, with a rate of 73, a PR interval of 0.16 second and a QRS interval of 0.08 second. The T_1 wave was flat and the T_2 and T_3 waves were inverted. The axis was normal. On the sixty-second day there was evidence of sinus arrhythmia, with a rate of 80, a PR interval of 0.14 second and a QRS interval of 0.09 second. The T_1 , T_2 and T_3 waves were upright and the axis was normal.

Studies of the Blood.—Values for each of the plasma lipids was diminished on the fifth day when the plasma was first examined. The allocation of total cholesterol showed a predominance of the free form. This altered ester cholesterol-total cholesterol ratio gradually changed with recovery, and the ratio was normal at the time of the patient's discharge from the hospital. The phospholipid and fatty acid fractions mirrored the gross changes shown by the variations in total lipids and cholesterol. The fatty acid fraction became normal sooner than the cholesterol fraction.

The value for nonprotein nitrogen was normal on the second day, but on the sixth day there was a marked retention of all the nitrogenous substances. The values for urea, uric acid and creatinine were each increased early and gradually returned to normal during convalescence. The amino-acid nitrogen content was

not altered. The value for blood sugar showed no definite correlation with the other laboratory or clinical observations. The high icteric index and bilirubin values showed a tendency to approximate a minimal ratio of 10 to 1 during convalescence.

Polymorphonucleosis was present on admission. The count dropped quickly to normal but rose again with the inception and for the duration of the pathologic process in the lungs. Marked secondary anemia was present at the onset of the edema; it responded slowly to treatment with ferric ammonium citrate (table). A differential count on the second day showed 64 per cent polymorphonuclears, 24 per cent lymphocytes, 8 per cent mononuclears, 2 per cent basophils and 2 per cent eosinophils; a differential count on the forty-first day showed 60 per cent polymorphonuclears, 25 per cent lymphocytes, 10 per cent mononuclears, 2 per cent eosinophils and 3 per cent basophils. The bleeding time was two minutes on the fourth day, four minutes on the tenth day and two and one-half minutes on the thirtieth day. The clotting time was two and one-half minutes on the tenth day and three minutes on the thirtieth day (capillary tube method). The plasma protein and the carbon dioxide capacity were 6.4 per cent and 52.3 per cent, respectively, on the thirtieth day. The Kahn test was negative.

Studies of the Urine.—The urine contained macroscopically visible bile on the second and the third day. The phenolsulphonphthalein test of renal function showed an excretion of less than 10 per cent in two hours on the ninth and the eleventh day. The first of these tests was performed on the day before the edema was noted. The urea clearance test gave supportive evidence of dysfunction of the kidneys. On the sixteenth day excretion of urea was 28 per cent of normal, and on the forty-seventh day, 50 per cent. The temporary urinary retention was in contrast with the small amount of albumin, red cells and casts found in the urine (table).

Examination of the Stools.—The stools for the first thirty-six hours were watery and contained a large amount of carbon tetrachloride, and the benzidine test for blood was positive. After the fourth day the stools were brown and formed.

COMMENT

A typical course following the experimental feeding of carbon tetrachloride to animals consists in vomiting, diarrhea, neurologic disturbances, jaundice and excretion of the poison through the lungs.⁴ Recovery from the poison is materially affected by the availability of calcium and dextrose.⁵ Postmortem examination of the animals at varying intervals after the ingestion of the poison reveals characteristic changes in the liver and minor changes in the lungs, kidneys and other organs.⁶ The microscopic changes in the kidneys are not outside the normal limits, as indicated by observations on control animals.⁶

4. Bollman, J. C., and Mann, F. C.: Experimentally Produced Lesions of the Liver, *Ann. Int. Med.* 5:699 (Dec.) 1931. Lamson et al.³

5. Minot, A. S., and Cutler, J. T.: Guanidine Retention and Calcium Reserve as Antagonistic Factors in Carbon Tetrachloride and Chloroform Poisoning, *J. Clin. Investigation* 6:369 (Dec.) 1928.

6. Gardner, G. H., et al.: Studies on the Pathological Histology of Experimental Carbon Tetrachloride Poisoning, *Bull. Johns Hopkins Hosp.* 36:107 (Feb.) 1925.

The course in our case of accidental poisoning followed closely that observed in animals during the acute stage. The prognosis cannot be determined until several years have elapsed in order to exclude the possible development of cirrhosis of the liver or other delayed pathologic changes resulting from the acute poisoning. However, the patient has been symptom-free for one-half year.

The laboratory data corroborate the clinical findings. The low values for the plasma lipids are consistent with the values in cases of jaundice due to damage of the liver.⁷ The diminished cholesterol ester-total cholesterol ratio was due largely to a decrease in the form of the ester and was related to the esterifying function of the liver.⁸ The increased nonprotein nitrogen content coincident with the diminished function of the kidneys shown by the tests indicate that a temporary upset in the function of the kidney occurred; but it also suggests possible close relations between the liver and the kidneys.⁹ The gradual approach of the icteric index and the bilirubin values during convalescence to a minimal ratio of 10 to 1 is consistent with the recovery of the function of the liver and the decreased stasis of bile pigment in the blood stream. Larger discrepancies between these values are found in jaundice associated with stasis of bile pigment in the blood stream or with the regurgitation of pigments other than bilirubin from the biliary system. A large amount of bile pigment in the blood stream interferes with the determination of hemoglobin by the usual colorimetric methods (Tallqvist and acid hematin).⁷ The presence of secondary anemia emphasizes the probable widespread effect of the circulating poison on all tissue with which it came in contact.

SUMMARY

A severe case of accidental poisoning with carbon tetrachloride occurring in a man addicted to alcohol is reported with laboratory data which indicated the widespread effect of the drug.

7. Lehnherr, Earl R.: The Value of Icteric Indices and Plasma Lipids in the Diagnosis of Jaundice, *New England J. Med.* **211**:487 (Sept. 13) 1934.

8. Thannhauser, S. J.: *Lehrbuch des Stoffwechsels und der Stoffwechselkrankheiten*, Munich, J. F. Bergmann, 1929, p. 486.

9. Pick, E. P.: Regulation of Water Metabolism, *Harvey Lectures*, 1929-1930, Baltimore, Williams & Wilkins Company, 1931, p. 25. Glaubach, S., and Molitor, H.: Die diuresefördernde Wirkung von Leberextrakt bei niereninsuffizienten Hunden, *Wien. klin. Wchnschr.* **42**:1437 (Nov. 7) 1929. Heyd, Charles G.: "Liver Deaths" in *Surgery of the Gallbladder*, *J. A. M. A.* **97**:1847 (Dec. 19) 1931. Schutz, Carl B.; Helwig, Ferdinand C., and Kuhn, Harold P.: A Contribution to the Study of So-Called Liver Death, *J. A. M. A.* **99**:633 (Aug. 20) 1932.

The values for each of the plasma lipids was low for the probable duration of the damage of the liver as evidenced by the clinical findings. The low values for total cholesterol and the diminished ester cholesterol-total cholesterol ratio are considered typical of jaundice due to damage of the liver.

The low lipid values occurred simultaneously with the retention of nitrogenous substances in the blood stream and may be significant in suggesting a close relationship between the functions of the liver and those of the kidneys.

Progress in Internal Medicine

DISEASES OF THE ADRENAL GLANDS

A REVIEW WITH SPECIAL REFERENCE TO THE
CLINICAL ASPECTS

EDWIN J. KEPLER, M.D.

ROCHESTER, MINN.

In their monograph on Addison's disease, Rowntree and Snell¹ in 1931 summarized the essential features of what was known about the physiology of the adrenal glands as follows:

Without discounting the value of studies on extirpation of the gland and on the preparation of glandular extracts, it must be said that the exact physiologic functions of the suprarenal gland in the intact animal are uncertain. Our exact knowledge of the physiology of the suprarenal glands can be expressed in two statements: the cortex of the gland is essential to life, and the medulla of the gland, although apparently not a vital organ, secretes a substance which is normally present in the blood stream and which has powerful pharmacodynamic properties. Of the multitude of other functions which have been suggested, few rest on adequate experimental grounds.

They referred the reader wishing to pass critical judgment on much that is written on the physiology of these glands in health and disease to the excellent reviews of Stewart,² Jaffe,³ Goldzieher⁴ and Biedl.⁵ At that time cortical extracts of the adrenal glands had been prepared by Rogoff and Stewart,⁶ by Hartman and his collaborators⁷ and by

From the Division of Medicine, the Mayo Clinic.

Dr. Albert M. Snell and Dr. Robert L. Parker assisted in the preparation of this manuscript.

1. Rowntree, L. G., and Snell, A. M.: A Clinical Study of Addison's Disease, Philadelphia, W. B. Saunders Company, 1931.

2. Stewart, G. N.: (a) Adrenalectomy and the Relation of the Adrenal Bodies to Metabolism, *Physiol. Rev.* **4**:163 (April) 1924; (b) Blood Studies in Dogs After Adrenalectomy, *J. Pharmacol. & Exper. Therap.* **29**:373, 1926.

3. Jaffe, H. L.: The Suprarenal Gland, *Arch. Path.* **3**:414 (March) 1927.

4. Goldzieher, M. A.: The Adrenals: Their Physiology; Pathology, and Diseases, New York, The Macmillan Company, 1929.

5. Biedl, Arthur: Die geschichtliche Entwicklung der Kenntnisse ueber die Nebenniere bis Addison (1855), *Janus* **15**:294, 1910.

6. Rogoff, J. M., and Stewart, G. N.: Studies on Adrenal Insufficiency: IV. The Influence of Intravenous Injections of Ringer's Solution upon the Survival Period in Adrenalectomized Dogs, *Am. J. Physiol.* **84**:649 (April) 1928; Studies on Adrenal Insufficiency in Dogs: V. The Influence of Adrenal Extracts on

Swingle and Pfiffner,⁸ and a number of patients with Addison's disease had been treated with some success by the administration of Swingle and Pfiffner's extract.⁹

Although Rowntree and Snell's¹ conclusions are in the main true today, some progress has been made, and it is my purpose in this paper to discuss briefly some phases of this progress which appear to be related to diseases of the adrenal glands.

In the following résumé of the newer work it has been necessary for the sake of proper perspective to review not only some of the older literature but also some material which may seem elementary to those primarily interested in endocrinology. Scant attention has been paid to the medullary portion of the gland. This was done deliberately, as very little could be added to what has already been written and ably reviewed many times. This does not imply that in the last five years no work of value has been done on the physiology of the adrenal medulla and its hormone, epinephrine. Many contributions have been made, especially on the relationship of the medulla and epinephrine to carbohydrate metabolism. This phase of the subject was reviewed in 1935 by Wilder and Wilbur.¹⁰ The pharmacologic properties of epinephrine are still a subject for study, and considerable work has been done on the relationship of the medulla to the problem of essential hypertension. Nevertheless, whether rightly or not, the general conception still obtains that the adrenal medulla is a relatively inert organ except in times of emotional stress when it discharges epinephrine. It appears likely that when some of the problems associated with the cortex are clarified more attention will again be directed to the medullary portion of the gland.

Survival Period of Adrenalectomized Dogs, *ibid.* **84**:660 (April) 1928; Suprarenal Cortical Extracts in Suprarenal Insufficiency (Addison's Disease), *J. A. M. A.* **92**:1569 (May 11) 1929.

7. (a) Hartman, F. A., and Brownell, Katherine A.: The Hormone of the Adrenal Cortex, *Science* **72**:76 (July 18) 1930. (b) Hartman, F. A.; Brownell, Katherine A.; Hartman, W. E.; Dean, C. A., and MacArthur, C. G.: The Hormone of the Adrenal Cortex, *Am. J. Physiol.* **86**:353 (Sept.) 1928. (c) Hartman, F. A.; MacArthur, C. G., and Hartman, W. E.: A Substance Which Prolongs the Life of Adrenalectomized Cats, *Proc. Soc. Exper. Biol. & Med.* **25**:69 (Oct.) 1927.

8. Swingle, W. W., and Pfiffner, J. J.: (a) An Aqueous Extract of the Suprarenal Cortex Which Maintains the Life of Bilaterally Adrenalectomized Cats, *Science* **71**:321 (March 21) 1930; (b) Further Observations on Adrenalectomized Cats Treated with an Aqueous Extract of the Suprarenal Cortex, *ibid.* **71**:489 (May 9) 1930; (c) The Revival of Comatose Adrenalectomized Cats with an Extract of the Suprarenal Cortex, *ibid.* **72**:75 (July 18) 1930.

9. Rowntree, L. G.; Greene, C. H.; Swingle, W. W., and Pfiffner, J. J.: Addison's Disease: Experiences in Treatment with Various Suprarenal Preparations, *J. A. M. A.* **96**:231 (Jan. 24) 1931.

10. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, *Arch. Int. Med.* **55**:304 (Feb.) 1935.

PHYSIOLOGY

If both adrenal glands are removed from animals a characteristic series of phenomena take place. In dogs, for example, nothing appears to happen for a period which varies from twelve hours to several days. The dogs then become easily fatigued and are apathetic; they refuse to eat and finally become exceedingly weak. The blood pressure, blood volume, basal metabolic rate, consumption of oxygen and body temperature decrease. Invariably the dogs lose weight; as they decline they usually go into a coma or a semistuporous condition, and just before death muscular twitchings and convulsions may appear. Death occurs in from three to eleven days after the operation. Considerable difference of opinion exists regarding the duration of this period of survival. Certain chemical changes take place which parallel the clinical picture. The concentration of the nonprotein nitrogen in the blood increases, largely as the result of an increase in the value for blood urea. The blood loses water and becomes thick and viscid. This loss of water is shown by an increased concentration of proteins in the blood and by an increase in the number of erythrocytes per unit of volume. Low values for blood sugar and symptoms of hypoglycemia are encountered frequently, and a remarkable series of changes in the concentration of various electrolytes takes place both in the blood and in the tissues. These changes will be considered in detail later. Following injection of the cortical hormone the animal improves, and the chemical constituents of the blood may again become normal.

Although practically all workers are agreed regarding the facts just stated, considerable difference of opinion has arisen regarding their interpretation. Four theories regarding the action of the cortical hormone have been propounded. Hartman, Brownell and Lockwood¹¹ demonstrated that the hormone is directly related to muscular fatigue and that it prevents the diminished resistance to cold and heat encountered in adrenalectomized animals. Because of its relationship to these factors as well as to others, such as metabolism, growth, fluid balance and probably renal function, they arrived at the conclusion that the cortical hormone is closely related to the function of all tissues and suggested that it might be considered as a general tissue hormone. Kendall, commenting on the work of Koelsche¹² (who demonstrated that following the injection of thyroxin the cortical hormone prevents the usual loss of nitrogen in both unilaterally and bilaterally adrenalect-

11. Hartman, F. A.; Brownell, K. A., and Lockwood, J. E.: Studies Indicating the Function of Cortin, *Endocrinology* **16**:521 (Sept.-Oct.) 1932.

12. Koelsche, G. A.: The Relation of the Suprarenal Cortical Hormone to Nitrogen Metabolism, *Proc. Staff Meet., Mayo Clin.* **9**:55 (Jan. 24) 1934.

tomized dogs), stated that Koelsche's results tended to support Hartman's point of view.

One of the earliest theories proposed to explain the action of the adrenal cortical hormone was that of Britton and Silvette¹³ who postulated that the adrenal cortex prepotently regulates carbohydrate metabolism and is chiefly concerned with the storage and utilization of carbohydrate. In January 1934 they reviewed the controversy which had developed regarding the function of the adrenal cortex and presented additional evidence to support their own contentions. They pointed out that the adrenalectomized rat suffers from a lack of dextrose and glycogen that becomes progressively more severe after adrenalectomy and parallels the development of the symptoms. (This is not in accord with the findings of Swingle, which will be given later, who used dogs as experimental subjects.) Britton and Silvette further showed that the injection of epinephrine scarcely affects the level of blood sugar in animals with adrenal insufficiency even though the animals are in good condition. This was explained as being the result of depleted glycogen stores in the liver. They also found that the synthesis of glycogen which normally takes place following the injection of dextrose and sodium lactate does not occur in any significant degree in the adrenalectomized animal, and they again called attention to the fact that animals dying of adrenal insufficiency have convulsive seizures some time before death, a fact which could not be explained on the basis of decreased blood volume or circulatory failure. They disputed the evidence offered by Swingle that the dilution of blood in adrenalectomized animals does not occur without the administration of the hormone, and they found that the blood volume could readily be restored by the injection of saline solution but with no relief of symptoms. Satisfactory but temporary response was obtained on administration of solution of dextrose. They found, as did Swingle, a reduction in the blood volume of adrenalectomized animals, although to a lesser extent; in some animals there was no change, and in others the blood volume was elevated. A definite shift of the body fluids seemed to take place, the movement of fluids being from the blood toward the liver and muscles. In a more recent article Silvette¹⁴ stressed the shift in the water and chloride balance that occurs in adrenalectomized animals. This shift is manifested by an increased content of water in the liver and muscles and by a decreased concentration of chloride in the tissues. Silvette expressed the opinion that the lack of hormone

13. Britton, S. W., and Silvette, H.: On the Function of the Adrenal Cortex—General, Carbohydrate and Circulatory Theories, *Am. J. Physiol* **107**:190 (Jan.) 1934.

14. Silvette, Herbert: Chloride, Carbohydrate and Water Metabolism in Adrenal Insufficiency and Other Conditions, *Am. J. Physiol.* **108**:535 (June) 1934.

indirectly produces some fundamental condition or factor that is responsible for the shift in the water and chloride balance, and this factor seems to be a deficiency in dextrose and glycogen.

Swingle and Pfiffner and their associates¹⁵ were not impressed by the changes that take place in the carbohydrate metabolism of adrenalectomized animals. In a series of articles they expressed the view that the chief and perhaps the only function of the adrenal cortical hormone is the regulation and maintenance of the normal circulating volume of blood. As a result of their experiments they attempted to show that all other factors are secondary and dependent on the loss of ability to maintain the blood volume. They interpreted their results to indicate that in the absence of the hormone in the adrenalectomized dog fluid is continually lost from the circulation, presumably by transudation. As the result of an insufficiency of circulating fluid the blood pressure falls progressively, the blood becomes unduly concentrated and viscid, renal function fails, and circulatory failure ensues. Adrenalectomized animals, according to them, are apparently unable to draw fluid back through the walls of the capillaries into the blood stream.

Swingle and Pfiffner also pointed out the striking similarity between adrenal insufficiency and traumatic shock and they supported their view by demonstrating that adrenalectomized animals show an unusual sensitiveness to hemorrhage. The removal of 40 cc. of blood from the dogs on which they were experimenting, an amount which in a normal dog would cause no effect, produced profound shocklike effects which are explained by the inability of the animal to restore its blood volume. In the normal mechanism of dilution the rôle of the adrenal cortex thus appears to be that of a mobilizer of water and salt, so that the saline solutions of the tissues and interstitial spaces become available for transfer to the blood stream. In the absence of the cortical hormone such transfer does not occur. In their more recent articles,¹⁶ Swingle, Pfiffner and others devoted considerable attention to the part played by sodium chloride in adrenal insufficiency, and they pointed out that the experimental feeding of sodium chloride to adrenalectomized ani-

15. (a) Swingle, W. W.; Pfiffner, J. J.; Vars, H. M.; Bott, P. A., and Parkins, W. M.: The Function of the Adrenal Cortical Hormone and the Cause of Death from Adrenal Insufficiency, *Science* **77**:58 (Jan. 13) 1933. (b) Swingle, W. W.; Pfiffner, J. J.; Vars, H. M., and Parkins, W. M.: The Effect of Hemorrhage on the Normal and Adrenalectomized Dog, *Am. J. Physiol.* **107**:259 (Feb.) 1934; (c) The Effect of Fluid Deprivation and Fluid Intake upon the Revival of Dogs from Adrenal Insufficiency, *ibid.* **108**:144 (April) 1934; (d) The Effect of Sodium Chloride Administration upon Adrenalectomized Dogs not Receiving Extract, *ibid.* **108**:159 (April) 1934.

16. Swingle, W. W.; Vars, H. M., and Parkins, W. M.: A Study of the Blood Volume of Adrenalectomized Dogs, *Am. J. Physiol.* **109**:488 (Sept.) 1934. Swingle, Pfiffner, Vars and Parkins.^{15b}

imals which were not receiving cortical extract somewhat prolonged the interval between the time that injections of extract were stopped and adrenal insufficiency developed. They concluded that sodium chloride could not be regarded as an effective substitute for cortical hormone in the bilaterally adrenalectomized dog since it was necessary to inject cortical extract in order to save the animals when symptoms sooner or later developed. Swingle and Pfiffner then investigated the water balance and fluid exchange in adrenalectomized dogs which were not receiving cortical extract. Their results indicated that the animals first exhibited a negative water balance and lost more fluids than they took in, and then that the normal exchange of fluid between the blood stream and tissues was upset and transudation from tissues to interstitial spaces impaired, since under these circumstances fluid and salt are not freely mobile. They were of the opinion that these factors taken together satisfactorily explained most if not all of the observed phenomena of adrenal insufficiency, but that taken singly neither factor was adequate to serve as an explanation.

Much of the credit for recognition of the very important part played by sodium chloride in adrenal insufficiency is due to Loeb and his collaborators.¹⁷ He made careful chemical studies of 3 patients with Addison's disease and found in all 3 a decrease in the total base which occurred largely at the expense of the sodium content. In all 3 cases the potassium content of the serum was either at a high normal level or definitely increased. Symptoms of adrenal insufficiency and the associated chemical changes disappeared in 1 case after the administration of sodium chloride. Loeb postulated that the syndrome of adrenal insufficiency may be directly concerned with this loss of base. (The work of Loeb will be referred to again in the discussion of the treatment of Addison's disease.) Loeb subsequently verified these results in dogs, and his work has since been confirmed by Harrop and his associates.¹⁸

Harrop¹⁸ found that stopping the injection of cortical extract in adrenalectomized animals in apparently good condition caused an immediate loss of sodium chloride before the excretion of nitrogen

17. (a) Loeb, R. F.: Chemical Changes in the Blood in Addison's Disease. *Science* **76**:420 (Nov. 4) 1932; (b) Effect of Sodium Chloride in Treatment of a Patient with Addison's Disease, *Proc. Soc. Exper. Biol. & Med.* **30**:808 (March) 1933. (c) Loeb, R. F.; Atchley, Dana W.; Benedict, Ethel M., and Leland, Jessica: Electrolyte Balance Studies in Adrenalectomized Dogs with Particular Reference to the Excretion of Sodium, *J. Exper. Med.* **57**:775 (May) 1933.

18. Harrop, G. A.; Soffer, L. J.; Ellsworth, Read, and Trescher, J. H.: Studies on the Suprarenal Cortex: III. Plasma Electrolytes and Electrolyte Excretion During Suprarenal Insufficiency in the Dog, *J. Exper. Med.* **58**:17 (July) 1933.

was much affected. The daily excretion of sodium chloride rose to double the original value, although after resumption of the use of the extract the excretion of this substance again returned to its former level. As a result of their experiments Harrop and his associates concluded:

A characteristic alteration in the electrolyte structure of the blood plasma of the suprarenalectomized dog occurs when injections of cortical extract are stopped. This alteration progresses during the course of the suprarenal insufficiency, parallel with the hemoconcentration and the loss in weight. When injections of cortical extract are resumed, the electrolyte structure returns to its original form, the alterations paralleling the dilution of the blood and the return of the body weight to its original level.

The hemoconcentration, with the resulting physiological changes which take place in the suprarenalectomized dog after the cessation of cortical extract injections, is associated with a loss of sodium and chloride, accompanied by their proper complement of body water, by way of the kidney. Since this effect is produced in the suprarenalectomized animal, well nourished and in excellent condition, solely by cessation of injections of the cortical hormone, and since the reverse process of repair of the electrolyte and water losses can be effected solely by resumption of extract injections, it follows that all of the observed phenomena are due to this cause, and to this alone. It can be concluded that one function of the cortical extract in the suprarenalectomized dog is that of participation in the regulation of the sodium and chloride metabolism, and consequently, of the balance and distribution of water. The loss of water, in the absence of the cortical hormone, is sustained partly by the blood plasma, but to a far greater extent by the interstitial body fluid. The available evidence points to the kidney as the focus of this regulatory function of the cortical hormone.

Zwemer and Sullivan,¹⁹ working with approximately 45 cats, investigated the chronological order of the changes in the chemical constituents of the blood which occur in cases of adrenal insufficiency and in general confirmed the work of Loeb and Harrop. They stated that adrenalectomy is followed by an early loss of sodium, reflected in a lowered carbon dioxide-combining power and in an increase in the values for potassium and nonprotein nitrogen of the blood. Chemically the syndrome of adrenal insufficiency seemed to Zwemer²⁰ to be a disturbance in the metabolism of salt and water, with loss of water and depletion of sodium and blood chlorides together with an increase of potassium in the blood. The injection of an extract of adrenal cortex into adrenalectomized animals was found to bring about a reversal of the chemical changes that occurred in animals with adrenal insufficiency, in addition to affecting the observable symptoms favorably. The suggestion was made that the adrenal cortex secretes something that enables the cells to metabolize salts and water.

19. Zwemer, R. L., and Sullivan, R. C.: *Blood Chemistry of Adrenal Insufficiency in Cats*, *Endocrinology* **18**:97 (Jan.-Feb.) 1934.

20. Zwemer, R. L.: *The Adrenal Cortex and Electrolyte Metabolism*, *Endocrinology* **18**:161 (March-April) 1934.

Gilman²¹ has presented the results of some very interesting experiments which demonstrate the effect in dogs of the loss of sodium without a concomitant loss of water or potassium. Using the method of Darrow and Yannet,²² Gilman injected 100 cc. per kilogram of body weight of isotonic solution of dextrose into the peritoneal cavity of dogs. The solution then attained osmotic equilibrium with its surroundings. After six hours complete equilibration had taken place before there was appreciable absorption of fluid by the dextrose solution, which by this time was a protein-free fluid that had a composition almost identical with that of extracellular fluid and contained a large amount of sodium. The fluid was then withdrawn by paracentesis. By this ingenious method there was produced a loss of sodium into the peritoneal cavity which was not accompanied by a loss of fluid. Immediately after withdrawal of the fluid studies of the chemical constituents of the blood were made, and the animals were subjected to slight hemorrhage which lowered the blood pressure to shock level. It was found that a marked fall occurred in the concentration of sodium and in the osmotic pressure of the serum. A shift of water into the cells in order to maintain osmotic equilibrium resulted in marked depletion of the extracellular fluid, as evidenced in the circulation by an increase in the specific gravity of its serum and by a fall in the blood pressure. This was in marked contrast to the results obtained after bleeding normal dogs to this extent. The intravenous injection of a 30 per cent solution of sodium chloride to replace the amount of sodium lost produced dramatic effects: The blood pressure returned to normal and the animal recovered immediately from the symptoms of shock and was ambulatory in a few hours. Gilman concluded from the similarity of behavior between his animals and adrenalectomized dogs that a similar shift in water occurs in the latter and that this shift accounts for the circulatory phenomena observed in adrenal insufficiency.

While these investigations on the function of the cortical hormone were in progress, Kendall and his associates²³ were directing their efforts to a chemical study of the hormone itself. In April 1934 he and his associates announced the isolation from the adrenal cortex of a crystalline form of the hormone which was essential to life. Further

21. Gilman, Alfred: Experimental Sodium Loss Analogous to Adrenal Insufficiency: The Resulting Water Shift and Sensitivity to Hemorrhage, *Am. J. Physiol.* **108**:662 (June) 1934.

22. Darrow, D. C., and Yannet, H., quoted by Gilman.²¹

23. Kendall, E. C.; Mason, H. L.; McKenzie, B. F.; Myers, C. S., and Koelsche, G. A.: Isolation in Crystalline Form of the Hormone Essential to Life from the Suprarenal Cortex: Its Chemical Nature and Physiologic Properties, *Proc. Staff Meet., Mayo Clin.* **9**:245 (April 25) 1934. Kendall, E. C.: Suprarenal Cortical Hormone, *Minnesota Med.* **18**:71 (Feb.) 1935.

studies on the chemical formula and physiologic activities of this substance are in progress.

In the preceding paragraphs a brief summary of some of the work being done on the physiology of the cortex of the adrenal glands has been presented. It is important to bear in mind in evaluating this experimental work that considerable differences exist in the behavior of various species and even in members of the same species after adrenalectomy. For example, it has been possible to maintain some dogs in good health for long periods by the injection of saline solution alone. Other dogs react unfavorably almost immediately after the cortical hormone has been withdrawn. To make matters more complicated, there is likely to be marked variation in the potency of different batches of the extract, and, as Kendall²⁴ pointed out in discussing Harrop's work, extracts standardized on the behavior of dogs may show marked variations in potency. Furthermore, there is considerable evidence to suggest that the adrenal gland may elaborate other hormones which as yet have not been isolated, and the impure extracts that are used for experimental purposes may possibly contain variable amounts of these additional hormones.

ADDISON'S DISEASE

In 1855 Addison²⁵ described the disease which now bears his name. In his original description he gave as the characteristic symptoms "anemia, general languor or debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of color in the skin." One year later Claude Bernard²⁶ excised the adrenal glands of animals and thereby produced fatal symptoms which he thought resembled those of Addison's disease.²⁷ In subsequent years the observations of both men were confirmed repeatedly, but except for a sharper delineation of the symptoms and pathologic findings no advance of phenomenal importance was made in the diagnosis or treatment of Addison's disease for seventy-five years. During these years it was

24. Kendall, E. C.: *Tr. A. Am. Physicians* **49**:156, 1934.

25. Addison, Thomas: *A Collection of the Published Writings of the Late Thomas Addison*, London, The New Sydenham Society, 1868.

26. Bernard, Claude: *Compt. rend. Acad. d. sc.* **43**:422 and 542, 1856; *J. de physiol. de l'homme* **1**:160, 1858.

27. As Stewart^{2a} correctly pointed out, much of the earlier work on the effects of bilateral adrenalectomy in animals proved nothing except that the experimenter was a poor surgeon. For example, Stewart, commenting on without criticizing the data of Brown-Séquard, showed beyond any doubt that when Brown-Séquard announced that the adrenal glands were indispensable to life his conclusion could not have been anything except a lucky guess. The same remark would have been equally applicable to the work of Claude Bernard, whose animals following the removal of one adrenal gland lived about twenty-five hours. Nevertheless, Claude Bernard deserves credit for starting the physiologic ball rolling.

definitely established that tuberculosis or atrophy of the adrenal glands accounted for most cases of the disease, that the morbidity of the disease was largely the result of destruction of the cortex and that the medulla and its hormone epinephrine were of secondary importance. Treatment was most unsatisfactory, though there appeared to be some promise of success in the Muirhead regimen which was sponsored by Rowntree and Snell.¹ Following the announcement of preparations of active hormones of the adrenal gland by Swingle and Pfiffner^{8a} and by Hartman and Brownell^{7a} there was a marked revival of interest in this disease; diagnostic procedures of considerable value have been developed, and satisfactory therapeutics appears to lie in the offing.

Symptoms.—Addison's²⁵ original and now classic description of the symptoms could scarcely be improved, and these symptoms are so well known that they can be dismissed without much comment.

It is important to bear in mind that the symptoms of the disease observed in the stage of crisis are distinctly different and should be sharply differentiated from those which appear during the stage of chronicity. In crisis the symptoms apparently result from an acute deficiency of the cortical hormone; in chronicity, the residual symptoms which persist after treatment, namely, slight weakness and asthenia, lowered resistance, hypotension and pigmentation, may be in part the result of medullary deficiency. In crisis, because of the preponderance of gastro-intestinal symptoms, such as nausea, vomiting, diarrhea and abdominal pain, the clinical picture may even simulate acute abdominal disease.²⁸ Hiccup may be the first indication of the onset of crisis, and its importance as a manifestation of Addison's disease is often overlooked. The frequency of digestive disturbances in Addison's disease has been the subject of a recent study by Marañón and Arguelles.²⁹

Pathologic Physiology.—As a result of recent physiologic studies a closer correlation has been established between experimental adrenal insufficiency and Addison's disease. However, Addison's disease in its entirety has never been produced experimentally in laboratory animals.³⁰

28. I recall with great vividness a case in which an erroneous diagnosis of subacute cholecystitis was made. The patient, an inmate of a large general hospital, died during the course of an attempt to remove the gallbladder. At necropsy two large caseous adrenal glands were the only features of consequence observed.

29. Marañón, G.; Sala, P., and Arguelles, G.: Digestive Symptoms in Chronic Suprarenal Insufficiency (Addison's Disease), *Endocrinology* **18**:497 (July-Aug.) 1934.

30. Rogoff (Proc. Soc. Exper. Biol. & Med. **29**:1240 [June] 1932) by means of subtotal ligation of the adrenal vessels has attempted with some success to reproduce atrophy of the adrenal glands comparable to that which occurs in some cases of Addison's disease. Clinical symptoms of subacute or chronic adrenal insufficiency appeared in some animals. The author did not state whether or not pigmentation resulted.

Adrenalectomized animals can be kept in perfect health over an indefinite period by replacement therapy, supplemented possibly by the addition of a liberal amount of sodium chloride to the diet. These animals breed and lactate and to all intents and purposes seem entirely normal. In spite of the best treatment available at present, however, patients with Addison's disease are rarely entirely normal: Pigmentation exists, the blood pressure remains low, and they usually lack normal vigor and stamina.

The recognition of the relationship of the disturbance of the metabolism of electrolytes to adrenal insufficiency marks a distinct advance in the knowledge of the pathologic physiology of Addison's disease. The striking effects of Ringer-dextrose solution in prolonging the life of adrenalectomized animals beyond the expected period of survival were demonstrated as early as 1925 by Rogoff and Stewart,³¹ and their results were confirmed by Banting and Gairns³² in the following year. Using saline solutions alone, Marine and Baumann³³ obtained similar results in similar experiments. Furthermore, Baumann and Kurland³⁴ noted a decrease of as much as 15 per cent in the sodium content of the blood of adrenalectomized rabbits. Clinicians were also aware of the therapeutic value of administering saline and dextrose solutions in the treatment of the "dehydration" that occurred during crises of Addison's disease. Although these facts were known, they excited little interest or comment until their significance was appreciated and demonstrated by Loeb and Harrop. Loeb^{17a} reported complete analyses of the inorganic base in the serum of 3 patients. In all 3 there was marked reduction in the values for sodium and the chlorides and an increase in the content of potassium in the serum. These chemical values were also studied in adrenalectomized dogs,^{17c} and these animals were found in periods of adrenal insufficiency to excrete an abnormal amount of sodium in the urine and to show a corresponding reduction in the values for sodium and chlorides in the serum. Harrop,¹⁸ working independently, also found in adrenalectomized animals that the total base of the blood serum

31. Stewart, G. N., and Rogoff, J. M.: Studies on Adrenal Insufficiency, *Proc. Soc. Exper. Biol. & Med.* **22**:394 (April) 1924-1925. Rogoff, J. M., and Stewart, G. N.: Studies on Adrenal Insufficiency: VIII. The Survival Period of Untreated Adrenalectomised Cats, *Am. J. Physiol.* **88**:162 (Feb.) 1929.

32. Banting, F. G., and Gairns, S.: Suprarenal Insufficiency, *Am. J. Physiol.* **77**:100 (June) 1926.

33. Marine, David, and Baumann, E. J.: Duration of Life After Suprarenal-ectomy in Cats and Attempts to Prolong It by Injections of Solutions Containing Sodium Salts, Glucose, and Glycerol, *Am. J. Physiol.* **81**:86 (June) 1927.

34. Baumann, E. J., and Kurland, Sarah: Changes in the Inorganic Constituents of Blood in Suprarenalectomized Cats and Rabbits, *J. Biol. Chem.* **71**:281 (Jan.) 1927.

was reduced largely at the expense of sodium and that the values for serum calcium, potassium and magnesium were increased.

Proof of the relationship between the sodium content of the serum and adrenal insufficiency was finally established by Loeb,^{17a} who gave a patient with Addison's disease additional salt by mouth. Marked improvement in the clinical condition took place. The administration of salt was then stopped because of the appearance of edema under the eyes, and five days later the patient was precipitated into a typical addisonian crisis. Studies of the total base of the serum showed the sodium content to be reduced. The administration of sodium chloride, even though no cortical hormone was given, brought about prompt improvement in the patient's condition, and the values for the electrolytes of the blood became normal. These results have since been confirmed by Harrop and his associates,³⁵ so that it is reasonably well established that the abnormal behavior of the serum electrolytes is of fundamental significance in the pathologic physiology of Addison's disease and that this abnormality in patients is manifested during periods of relapse or crisis by a decreased concentration of the sodium and chloride ions in the serum, a decreased concentration of the titratable total base and an increase in the concentration of the potassium ions. The values for calcium and magnesium are increased or unchanged.

The cause of the pigmentation that occurs with great regularity in Addison's disease is still a mystery. It is known that the pigmentation results from the deposition of an abnormal amount of melanin, which is the normal pigment of the skin. The metabolism of melanin is still unexplored. Snell and Rowntree³⁶ reviewed the literature on the subject in 1929. The various theories were reviewed at that time, and since the article was written no contributions of note have come to my attention. Harrop and his collaborators³⁵ as well as many of the earlier writers, thought that pigmentation may be a manifestation of medullary insufficiency.

Pathology.—It is generally stated that tuberculosis of the adrenal glands accounts for from 80 to 90 per cent of cases of Addison's disease. Atrophy of these glands explains the vast majority of the remainder. It is interesting to note that this ratio seems to be changing. Snell³⁷ stated that: "A search of the literature revealed that in seventeen of the thirty recently reported necropsies, in cases of Addison's

35. Harrop, G. A.; Weinstein, Albert; Soffer, L. J., and Trescher, J. H.: The Diagnosis and Treatment of Addison's Disease, *J. A. M. A.* **100**:1850 (June 10) 1933.

36. Snell, A. M., and Rowntree, L. G.: Addison's Disease with Anomalous Pigmentation, *Endokrinologie* **5**:303, 1929.

37. Snell, A. M.: The Treatment of Addison's Disease, *Proc. Staff Meet., Mayo Clin.* **9**:57 (Jan. 24) 1934.

disease which had been treated, atrophy of the suprarenal glands was present." According to these figures atrophy of the adrenal glands accounted for 57 per cent of the cases in which patients died and came to necropsy. As there is no good reason to presume that the adrenal glands are now being attacked by tuberculosis less frequently than in former years it would appear either that treatment is more effective in prolonging life in the group of patients whose condition is caused by adrenal tuberculosis or that these patients may be "protected to some extent by the survival of fragments of cortical tissue and cortical adenomas."³⁷ The tuberculous process appears to start either in the medullary or in the midcortical portion and then to advance toward the periphery. Adenomas of the cortex may or may not be involved. Presumably those adenomas that remain may have the capacity to function. In contradistinction to the tuberculous process, atrophy begins in the cortex and compresses the medulla. Fragments of medullary tissue may remain, but usually the entire gland is destroyed. The cause of the atrophy is entirely unknown. Occasionally Addison's disease is reported as being caused by extra-adrenal disease. A recent example was a case reported by Bicknell³⁸ in which malignant involvement of the solar plexus was found. Tuberculosis of the adrenal glands has been studied recently by Gsell and Uehlinger.³⁹ Thirty-five cases of bilateral total tuberculosis and 37 of unilateral or bilateral incomplete tuberculosis were analyzed. These writers concluded that the infection is hematogenous and originates in a primary or postprimary tuberculous focus. In a third of their cases the only active tuberculous process was in the adrenal glands. They stated that the infection probably begins during or after puberty and has a long period of development, during which the disease proceeds intermittently, the symptoms of Addison's disease beginning only after the period of glandular insufficiency. Barker⁴⁰ has made an excellent study of the pathologic anatomy of Addison's disease, and a comprehensive survey of the entire field of adrenal pathology, including tumors, may be found in the article by Fritz Paul.⁴¹

Diagnosis.—The diagnosis of a typical case of Addison's disease usually presents no difficulties. In doubtful cases, especially in those in

38. Bicknell, Franklin: Addison's Disease Due to Malignant Involvement of the Solar Plexus, *Brit. M. J.* **2**:206 (Aug. 4) 1934.

39. Gsell, O., and Uehlinger, E.: Tuberkulöser Morbus Addison. Stellung der Nebennierentuberkulose im Ablauf der tuberkulösen Infektion, *Beitr. z. Klin. d. Tuberk.* **83**:121, 1933.

40. Barker, N. W.: The Pathologic Anatomy in Twenty-Eight Cases of Addison's Disease, *Arch. Path.* **8**:432 (Sept.) 1929.

41. Paul, Fritz: Die krankhafte Funktion der Nebenniere und ihr gestaltlicher Ausdruck, *Virchows Arch. f. path. Anat.* **282**:256 (Oct. 17) 1931.

which there is no pigmentation, three procedures have proved to be of distinct value: 1. Biopsy of the skin may be of material aid in excluding other causes of pigmentation, such as those produced by arsenic, silver, hemachromatosis and acanthosis nigricans. Biopsy, however, will not positively identify the pigmentation of Addison's disease as such. 2. Camp, Ball and Greene⁴² were able to identify calcium in the adrenal glands by making roentgenograms with the patient in the oblique position.⁴³ Positive findings were disclosed in a series of 6 of 23 consecutive patients. In interpreting such roentgenograms it is important that one be not misled by calcification of the adjacent lymph nodes or cartilages of the ribs. Apparently normal persons occasionally present roentgenographic findings corresponding with those seen in Addison's disease. It is not known whether adrenal insufficiency will or will not subsequently develop in such persons. 3. Harrop and his associates³³ suggested the use of a salt-free diet to aid in the diagnosis of Addison's disease. In normal persons with intact adrenal glands no symptoms result from deprivation of salt, and only minor changes occur in the chemical constitution of the blood. However, in a patient with Addison's disease this deprivation is almost certain to precipitate a state of "acute relapse," with its attendant blood picture of acute adrenal insufficiency. The value of this test has been observed at the Mayo Clinic in several cases. In one patient, under observation at the present time, pigmentation was so slight that one could not be sure of its presence. Evidence of calcification was absent in roentgenograms of the adrenal areas. Fifty-four hours after the patient was placed on a salt-free diet the diagnosis of Addison's disease was definitely established. This test when used in conjunction with roentgenographic studies of the adrenal areas should be of great value, not only in cases in which pigmentation is lacking, but also in cases in which the patient is a member of one of the darker skinned races, in whom the presence of pigmentation is notoriously difficult to evaluate. It is important to call attention to the fact that this diagnostic procedure is not without considerable danger and should not be undertaken unless the physician is familiar with the signs and symptoms of acute adrenal insufficiency and has at hand a liberal supply of the cortical hormone and the means of administering treatment promptly should the symptoms of crisis appear.

42. Camp, J. D.; Ball, R. G., and Greene, C. H.: Calcification of the Suprarenal Glands in Addison's Disease: Roentgenographic Study, *Am. J. Roentgenol.* **28**:594 (Nov.) 1932.

43. As early as 1914 Rolleston and Boyd (Rolleston, H. D., and Boyd, E. J.: *Brit. J. Child. Dis.* **11**:105 [March] 1914) detected calcification in the adrenal glands by roentgenographic methods. The technic was perfected by Camp and his associates.

Treatment.—It is unfortunate that at present there is no method by which minor degrees of adrenal cortical insufficiency can be measured. On that account the treatment of Addison's disease is still somewhat crude and comparable to what the treatment of diabetes would be without methods for determining the sugar content of the urine and blood. Theoretically the treatment should be simple, and it should consist essentially in supplying the missing hormone and maintaining the normal chemical pattern of the blood. In practice these aims are partially accomplished by the injection of cortical hormone and by the use of additional salt in the diet. Recently the value of commercial preparations of the hormone has been vigorously challenged by Rogoff,⁴⁴ and there is considerable difference of opinion regarding the relative merits of the use of sodium chloride and the hormone. It is difficult to reconcile Rogoff's views with present clinical experience and with the earlier reports of the efficacy of the cortical hormone.⁴⁵ When those reports were written it was generally thought that the value of cortical hormone in the treatment of Addison's disease had been established. It is important to bear in mind that the poor results which Rogoff reported were obtained with commercial extracts. There seems to be no doubt of the fact that different lots of the available commercial preparations may vary in potency; and it is unfortunate that such is the case. The fault, however, appears to lie not with the hormone itself but with methods of preparing and standardizing it. Until some simple and rapid method of measuring cortical adrenal activity is available it appears likely that there will be trouble in preparing standard potent extracts. Cantor and Scott⁴⁶ recently reported a case which illustrates the value of the hormone. Their patient was revived from a state of crisis no less than fourteen times in twenty-six months by its use.

44. Rogoff, J. M.: The Adrenal Cortical Hormone: Experiments with a Commercial Adrenal Extract (Eschatin), *J. A. M. A.* **103**:1764 (Dec. 8) 1934.

45. Rowntree, L. G.; Greene, C. H.; Swingle, W. W., and Pfiffner, J. J.: The Treatment of Patients with Addison's Disease with the Cortical Hormone of Swingle and Pfiffner, *Science* **72**:482, 1930; Addison's Disease: Experiences in Treatment with Various Suprarenal Preparations, *J. A. M. A.* **96**:231 (Jan. 24) 1931. Rowntree, L. G.; Greene, C. H.; Ball, R. G.; Swingle, W. W., and Pfiffner, J. J.: Treatment of Addison's Disease with the Cortical Hormone of the Suprarenal Gland: Summary of Immediate Results in Twenty Cases Treated with the Preparation Made by Swingle and Pfiffner, *ibid.* **97**:1446 (Nov. 14) 1931. Swingle, W. W., and Pfiffner, J. J.: The Adrenal Cortical Hormone, *Medicine* **11**:371 (Dec.) 1932. Hartman, F. A.: Studies on the Function and Clinical Use of Cortin, *Ann. Int. Med.* **7**:6 (July) 1933.

46. Cantor, M. M., and Scott, J. W.: Treatment of Addison's Disease with an Extract of the Adrenal Gland: Report of a Case in Which Experimental Relapses and Remissions Were Brought About, *Endocrinology* **18**:341 (May-June) 1934.

Largely as the result of the investigations of Loeb and Harrop the place of sodium chloride has been definitely established in the treatment of Addison's disease. Harrop and his associates³⁵ reported the cases of 4 patients with the disease in its chronic phase who were able to remain in reasonably good health by the addition of sodium chloride to their diet. These patients were not given the hormone. As a result of previous experience with cases in which patients were treated with the hormone alone, Harrop and his associates were led to believe that the clinical value of injections of cortical hormone during periods of remission had not been demonstrated. They observed no effect on the hypotension or pigmentation and were not convinced of the efficacy of the hormone in maintaining nutrition and weight; however, they saw no danger in its use. They felt that its chief value was in the treatment of the patient in a state of acute relapse, when its use was of definite help and might be of vital importance.

Snell⁴⁷ has recently reviewed the treatment of Addison's disease with sodium chloride and cortical hormone. He emphasized the necessity for individualizing treatment and pointed out the well established fact that treatment of the patient either in a state of crisis or in one bordering on crisis is considerably different from that used during periods of latency. The treatment of a patient in a state of acute relapse, according to Snell, is of the same magnitude and importance as the treatment of a patient with diabetic acidosis or coma. Cortical hormone is unquestionably necessary here and should be given preferably in small repeated doses rather than in one large dose. From 5 to 20 cc. or more should be given intravenously or intramuscularly; in the presence of acute infection larger doses may be necessary. The intravenous administration of physiologic solution of sodium chloride and solutions of dextrose, Snell stated, is an almost indispensable adjunct. After the patient has been brought out of a state of crisis, further treatment should depend on his condition and the level of the blood chlorides and blood urea. He pointed out that most, if not all, of the failures in the treatment of crisis may be attributed to the administration of an insufficient amount of hormone. He recognized that some patients can get along with salt alone; from 6 to 15 Gm. of salt is added to the diet, which may be given in enteric-coated capsules. (Since his article has been published, it has been the practice at the Mayo Clinic to give sodium chloride by mouth in the form of a physiologic solution. Salt also may be given in milk or with lemon juice. Enteric-coated capsules are expensive and in some cases cause gastro-intestinal disturbances.) Other patients do better

47. Snell, A. M.: The Diagnosis and Treatment of Addison's Disease with Reference to a Series of Forty-Six Patients Treated with the Suprarenal Cortical Hormone, *Internat. Clin.* 3:46 (Sept.) 1934.

on a regimen of sodium chloride plus small amounts of hormone. Snell pointed out the advisability of determining the necessity for use of the hormone before the patient is dismissed from the hospital, and he stressed the necessity of instructing such a patient regarding the dangers of crisis and the need of prompt and energetic treatment should relapse occur.

(Experience in 3 cases observed at the Mayo Clinic, reports of which have not yet been published, indicates that in certain instances at least continued use of the hormone is as necessary as the use of saline solutions. One of the patients was very sensitive to withdrawal of the hormone, even though the use of salt was continued. When administration of the hormone was discontinued anorexia, abdominal pain and asthenia developed, and these symptoms were relieved only by injection of the hormone.)

Wilder⁴⁸ recently published observations indicating that extracts of the anterior lobe of the pituitary body might be of some value in the treatment of Addison's disease. One patient, who remained in the state of invalidism in spite of the use of cortical hormone and saline solution, received considerable benefit, as shown by a gain in weight and strength when extract of the anterior lobe of the pituitary gland was added to the treatment. Other patients seem to be less sensitive to deprivation of salt while receiving the pituitary extract. This adjunct to treatment is based on the work of Kraus,⁴⁹ who observed regressive changes in the chromophil cells in the pituitary body in cases of Addison's disease.

Most experienced clinicians would probably agree that the general principles underlying the present treatment of Addison's disease could be summarized as follows:

1. The patient in a state of crisis is not likely to be overtreated. In such instances large amounts, from 10 to 50 cc. or more of the hormone, should be used in conjunction with saline solution given, if necessary, intravenously. The dose should be increased until an effect is achieved.

2. No hard and fast rule can be laid down for the treatment of the patient in the stage of chronicity. Many patients apparently get along satisfactorily with the aid of additional salt in the diet. In many such cases the use of small daily doses of the hormone (2 cc., for example) is unnecessary. However, such small doses probably do no harm except to deplete the patient's pocketbook.

3. The use of the hormone in its present form should as a rule be restricted to those patients who are in a state of crisis and to those

48. Wilder, R. M.: The Use of Anterior Lobe Pituitary Extract in the Treatment of Addison's Disease, *Proc. Staff Meet., Mayo Clin.* **9**:689 (Nov. 14) 1934.

49. Kraus, E. J.: Zur Pathologie des Morbus Addisoni (Befundi in Hypophyse und Nebennieren), *Beitr. z. path. Anat. u. z. allg. Path.* **78**:283, 1927.

occasional patients who cannot get along without the hormone and the are in a state that has been termed "chronic relapse."

4. The general condition of the patient and the status of the blood chlorides and blood urea can be used as a guide in management. Consideration of the changes in the weight of the patient is of great importance. Loss of weight can never be safely disregarded, and a patient who is adequately treated should gain weight or at least maintain his weight at a constant level.

Results of Treatment.—To evaluate the results of treatment it is necessary to bear in mind the fact that some patients who are not treated live for a remarkably long time. Snell⁵⁰ recently reported a case in which pigmentation was first noticed in 1917 and a definite positive diagnosis of Addison's disease was made in 1923. In a study of 566 cases reported in the literature prior to 1929, Guttman⁵¹ found that the average length of life of patients with Addison's disease caused by atrophy of the adrenal glands was 34.02 ± 4.4 months and that the average duration of the disease caused by tuberculosis of the adrenal glands was 13.315 ± 2.55 months. It is obvious that an insufficient length of time has passed to evaluate the results of treatment with present methods.

Lisser, Taylor and Leet⁵² reviewed the results of the use of cortical extracts in 100 cases. Three of the patients in this series were their own. They expressed the belief that a thorough clinical trial of the efficacy of cortical hormone must await its further concentration and purification. They commented on the magic effects following administration of cortical extract to patients in a state of crisis. The authors' 3 patients died because of the administration of inadequate amounts of the hormone. The authors commented on the high cost of the extracts and concluded that the purchase of an adequate amount would mean an annual expenditure of from \$500 to \$1,500 per patient. It is obvious that only the rich can afford to have Addison's disease.

Results of treatment were reviewed by Harrop and his associates³⁵ in June 1933. They treated 13 patients over a period of two and a half years. Of these 13 patients, 7 died. One patient died as a result of inadequate treatment and 2 patients had advanced tuberculosis elsewhere in the body. In the remaining 4 cases suprarenal cortical atrophy

50. Snell, A. M.: Addison's Disease of Unusually Long Duration, Proc. Staff Meet., Mayo Clin. 9:303 (May 23) 1934.

51. Guttman, P. H.: Addison's Disease: A Statistical Analysis of Five Hundred and Sixty-Six Cases and a Study of the Pathology, Arch. Path. 10:742 (Nov.); 895 (Dec.) 1930.

52. Lisser, H.; Taylor, F. B., and Leet, N. B.: The Adrenal Cortical Therapy of Addison's Disease in Clinical Practice, Endocrinology 18:333 (May-June) 1934.

on a present. The patients who were living had had the disease from point to sixteen months and were in reasonably good health. Snell,³⁷ in January 1934, reported the results of treatment in 48 patients with Addison's disease seen at the Mayo Clinic from May 1930 to January 1934. Thirty-two patients had died, 12 of whom received what was thought to be adequate treatment. Sixteen patients were living; of these, 7 were in good condition for more than a year, 6 were reported as doing well although treatment had been in progress for less than six months, and 3 were in poor condition because of their inability to obtain adequate supplies of the hormone.

It is evident from these reports that the treatment of Addison's disease still leaves much to be desired so far as the expectancy of life is concerned. Nevertheless, the sense of well-being, the increased vigor and the improvement in the mental status of the patient make treatment worth while. It seems likely that better results will be achieved in the near future as a result of improved methods of treatment and more refined preparation of the hormone.

DISEASES CHARACTERIZED BY CORTICAL OR MEDULLARY HYPERFUNCTION

It will be recalled that the adrenal gland consists of two portions which differ in origin, structure and function. The cortex or outer portion arises from the embryonic buds of celomic epithelium that project from the region of the root of the mesentery into the mesenchyma mesial to the wolffian bodies. From the mesial side of the wolffian bodies the undifferentiated primitive sex glands take their origin and after further development become differentiated into ovaries or testes and subsequently descend to the pelvis or scrotum. The intimate embryologic relationship of the adrenal cortex and sex glands assumes importance because adrenal cortical tumors usually are associated with changes in the secondary sexual characteristics. The medullary portion of the adrenal gland takes its origin in the mass of cells that arise from the abdominal portion of the sympathetic nervous system. At the end of the first month of fetal life the strands of these cells penetrate into the adrenal cortex where they become concentrated and after further differentiation lose their resemblance to nerve cells and form the adult suprarenal medulla.

When classified functionally the following disturbances in the adrenal glands are theoretically possible: (1) cortical hyperfunction, (2) cortical hypofunction, (3) medullary hyperfunction and (4) medullary hypofunction. One can conceive of mixed clinical pictures in which hyperfunction of the cortex could be associated with hypofunction of the medulla and vice versa, but as yet no clearcut clinical examples of

this have been described. Three of the four theoretical possibilities have been encountered clinically, namely, cortical (and medullary?) insufficiency, which is exemplified by Addison's disease; medullary hyperfunction, which is seen in the hyperfunctioning medullary tumors, such as paraganglioma or pheochromocytoma, that produce paroxysmal hypertension or continuous hypertension often indistinguishable from essential hypertension, and finally, cortical hyperfunction, which is presumed to produce the so-called adrenal cortical syndrome. This syndrome has been called by various writers suprarenal virilism, the genitosuprarenal syndrome, adrenal hirsutism, *le syndrome génito-surrénal* and other similar names. None of these terms is entirely satisfactory. In this paper we shall speak of it as the adrenal cortical syndrome.

Symptoms in the Adrenal Cortical Syndrome.—The symptoms vary depending on the age and sex of the patient and the nature of the pathologic process in the adrenal glands. Unquestionably it occurs in males, although in the majority of cases reported the patients have been female. Before puberty the disease is characterized in boys by precocious somatic and sexual development. Lisser⁵³ recently reviewed the literature on cortical adrenal tumor in boys and found 8 unquestionable cases and 2 additional cases in which the disease probably was present. Lisser reported a ninth case in which a boy aged 4 years had a bone age of a child of 12 years, the genitalia of a man and semen-containing spermatozoa. Diagnosis was made by roentgenograms, and a tumor of the left adrenal gland was successfully removed. Amelioration of the symptoms resulted. In 1927, Gordon and Browder⁵⁴ reported a similar case; at necropsy carcinoma of the left adrenal gland was found. Unfortunately, in this case the pituitary body was not examined. The disease occurs much less frequently in men. A few cases, however, have been reported, notably by Weber,⁵⁵ Holl⁵⁶ and Broster and Vines.⁵⁷ In these cases there seemed to be a definite degree of feminization, resulting in a female type of obesity associated with well developed breasts which were

53. Lisser, H.: Successful Removal of Adrenal Cortical Tumor Causing Sexual Precocity, *Tr. A. Am. Physicians* **48**:224, 1933.

54. Gordon, M. B., and Browder, J. E.: Suprarenal Carcinoma with Pubertas Praecox in a Boy Three Years of Age, *Endocrinology* **11**:265 (July-Aug.) 1927.

55. Weber, F. P.: Cutaneous Striae, Purpura, High Blood-Pressure, Amenorrhoea and Obesity, of the Type Sometimes Connected with Cortical Tumours of the Adrenal Glands, Occurring in the Absence of Any Such Tumour—With Some Remarks on the Morphogenetic and Hormonic Effects of True Hypernephromata of the Adrenal Cortex, *Brit. J. Dermat.* **38**:1 (Jan.) 1926.

56. Holl, Gundakr: Zwei männliche Fälle von Nebennierenrindentumoren mit innersekretorischen Störungen, *Deutsche Ztschr. f. Chir.* **226**:277, 1930.

57. Broster, L. R., and Vines, H. W. C.: *The Adrenal Cortex: A Surgical and Pathological Study*, London, H. K. Lewis & Company, Ltd., 1933.

was able of secreting milk. In some instances loss of libido and atrophy of the penis and testes were present. In girls before the age of puberty, obesity, premature sexual development and menstruation, enlargement of the breasts, hypertrophy of the clitoris and hirsutism are the usual symptoms. Representative cases in which a cortical tumor was successfully removed have been reported by Collett⁵⁸ and by Kennedy and Walters.⁵⁹

In the majority of cases the disease occurs in women and is characterized by an abnormal growth of hair of masculine distribution, amenorrhea, profound weakness, hypertension, peculiar swelling and high color of the face and often diabetes, which may be either latent or frank. Other symptoms, such as purplish striae of the skin, osteoporosis and such psychologic changes as loss of modesty and lack of interest in the male sex have been noted. Considerable variation in the presence and intensity of these symptoms may occur.

Symptoms may appear with surprising rapidity. In 1 case the face became so swollen within a period of three weeks that acute nephritis was suspected. Usually, however, the onset is more gradual, and it is only after the lapse of several months or longer that the change in the appearance of the patient becomes marked. Generally there is gain in weight, although in some cases reported this gain has not been marked, and the patient does not necessarily become obese. Likewise, the amount of hirsutism has been variable. In some cases the growth of hair on the face has been comparatively inconspicuous, and in others a fully developed beard has been present. Weakness, anorexia, hypertension and acne may be mild or absent.

Pathologic Findings.—Hyperfunctioning tumor of the adrenal cortex is present in the majority of cases of the adrenal cortical syndrome. In some cases the syndrome seems to be the result of unilateral or bilateral cortical hyperplasia and, finally, in a most interesting group of cases the syndrome has been present in disease of other glands of internal secretion, in which instances hyperplasia of the adrenal cortex has often been present.

Hyperfunctioning Cortical Tumors.—The older literature on the subject has been thoroughly reviewed by Glynn,⁶⁰ Bulloch and

58. Collett, Arthur: Genito-Suprarenal Syndrome (Suprarenal Virilism) in a Girl One and a Half Years Old, with Successful Operation, *Am. J. Dis. Child.* **27**:204 (March) 1924.

59. Kepler, E. J.; Kennedy, R. L. J.; Davis, A. C.; Walters, Waltman, and Wilder, R. M.: Suprarenocortical Syndrome and Pituitary Basophilism: Presentation of Three New Cases, *Proc. Staff Meet., Mayo Clin.* **9**:169 (March 21) 1934.

60. Glynn, E. E.: The Adrenal Cortex, Its Rests and Tumours: Its Relation to Other Ductless Glands, and Especially to Sex, *Quart. J. Med.* **5**:157 (Jan.) 1912.

Sequeira,⁶¹ Collett,⁵⁸ Gallais,⁶² Apert,⁶³ Holmes,⁶⁴ Rowntree and Ball,⁶⁵ and other writers. More recently, cases have been reported by Cecil,⁶⁶ Leshner,⁶⁷ Hicks⁶⁸ and Kolodny.⁶⁹ In Kolodny's case the tumor which was situated between the leaves of the mesentery was successfully removed. Death occurred, however, from metastasis. When the adrenal cortical syndrome is present and associated with a tumor of the adrenal cortex the relation of the symptoms to the tumor appears to be clearcut. If the tumor is removed successfully regression of symptoms takes place, and in 1 case at least, reported by Walters and me,⁵⁹ recurrence of the tumor was followed by recurrence of the symptoms in all essential features.

Cortical Hyperplasia.—Here the relationship of the pathologic findings to the clinical picture is by no means so clearcut as in the case of adrenal tumor. Diffuse hyperplasia of the adrenal gland may occur as an accidental finding in cases in which there is no evidence of any endocrine disorder. Cortical hyperplasia unquestionably accounts for the adrenal cortical syndrome in some cases. This was exemplified indisputably in a case reported by Davis and Walters⁵⁹ in which death occurred, and gross and microscopic examination of the entire endocrine system disclosed no other pathologic changes. Goldzieher⁷⁰ has reported cases in which a number of salient features of the adrenal cortical syndrome were present and were relieved by unilateral or partial bilateral adrenalectomy. The diagnosis in some of these cases is not clearcut, and it cannot be said with certainty that the pathologic changes were confined to the adrenal glands. It may be possible that such cases represent a milder degree or an incomplete form of cortical hyperfunction.

61. Bulloch, William, and Sequeira, J. H.: On the Relation of the Suprarenal Capsules to the Sexual Organs, Tr. Path. Soc. London **41**:189, 1905.

62. Gallais, Alfred: Le syndrome génito-surrénal; étude anatomo-clinique, Paris, Société de pédiatrie de Paris, 1912.

63. Apert, E.: Dystrophies en relation avec des lésions de capsules surrénales; hirsutisme et pregeria, Bull. Soc. de pédiat. de Paris **12**:501, 1910.

64. Holmes, Gordon: A Case of Virilism with a Suprarenal Tumor: Recovery After Its Removal, Quart. J. Med. **18**:143, 1925.

65. Rowntree, L. G., and Ball, R. G.: Diseases of the Suprarenal Glands, Endocrinology **17**:263 (May-June) 1933.

66. Cecil, H. L.: Hypertension, Obesity, Virilism and Pseudohermaphroditism as Caused by Suprarenal Tumors, J. A. M. A. **100**:463 (Feb. 18) 1933.

67. Leshner, F. G.: A Comparison of the Pituitary Basophilic Syndrome and the Adrenal Cortico-Genital Syndrome, Quart. J. Med. **4**:23 (Jan.) 1935.

68. Hicks, J. B.: Adenoma of the Adrenal Cortex (with Report of a Case), New England J. Med. **199**:1140 (Dec. 6) 1928.

69. Kolodny, Anatole: Suprarenal Virilism in a Woman (Tumor of an Extra-renal Suprarenal Rest), J. A. M. A. **102**:925 (March 24) 1934.

70. Goldzieher, M., and Koster, H.: Adrenal Cortical Hyperfunction, Am. J. Surg. **27**:93 (Jan.) 1935.

of adrenal cortex and its relation to intersexuality. After presenting a résumé of the signs and symptoms of the adrenal cortical syndrome they classified the syndrome as follows: (1) adrenal pseudohermaphroditism, which is the most complete form of the disease and develops in utero before sex organs have become differentiated; (2) adrenal virilism, which develops after puberty and is characterized by alteration in the form of the body and external sex organs, hypertrichosis of the male type and disturbances of sexual function, and (3) Achard-Thiers syndrome or the "diabetes of bearded women," which is a condition usually found at necropsy and consists essentially of adrenal hyperplasia associated with changes in the other ductless glands. They recommended unilateral adrenalectomy as a treatment for adrenal virilism, the results of which have been disappointing in the other two groups. They reported 10 cases of adrenal virilism. The ages of the patients varied from 15 to 29 years. All were treated by unilateral adrenalectomy with beneficial results. Broster and Vines stated that the microscopic evidence of hyperfunction of the adrenal glands can be demonstrated by the Ponceau-Fuchsin staining reaction even in the absence of gross or microscopic evidence of hyperplasia. This reaction was positive in all 10 cases and was found to be negative in normal adrenal glands. If this work can be confirmed it unquestionably marks a distinct advance in the study of adrenal pathology. It is difficult to correlate Broster and Vines' results with the well known physiologic fact that unilateral adrenalectomy in animals is without any demonstrable effect. However, adrenal virilism may be comparable to exophthalmic goiter, which is often benefited by removal of one lobe of the thyroid gland.

The adrenal cortical syndrome may occur with bilateral adrenal cortical hyperplasia in association with disease of other glands of internal secretion, notably of the pituitary and the thymus. For example, in the syndrome which has been described by Cushing⁷² as pituitary basophilism and which in its clinical features if not identical at least has many points in common with the cortical adrenal syndrome, the cortices of the adrenal glands are frequently hypertrophied and may contain adenomas. It is possible in such cases that the hyperfunctioning baso-

71. Broster, L. R., and Vines, H. W. C.: *The Adrenal Cortex: A Surgical and Pathological Study*, London, H. K. Lewis & Company, Ltd., 1933, p. 94.

72. Cushing, Harvey: (a) *The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism)*, Bull. Johns Hopkins Hosp. **50**:137, 1932. (b) "Dyspituitarism": Twenty Years Later, with Special Consideration of the Pituitary Adenomas, Arch. Int. Med. **51**:487 (April) 1933. (c) *Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System*, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

philic tumor of the pituitary body might stimulate overactivity of the adrenal cortex. There is some experimental work to indicate that such might be the case. For example, Evans,⁷³ Collip and his associates,⁷⁴ and Houssay⁷⁵ have independently presented evidence indicating the existence of an adrenotropic hormone. Houssay, for instance, demonstrated that in hypophysectomized dogs the weight of the adrenal glands decreased 38 per cent and was associated with atrophy and vacuolar degeneration of the cortex and that the administration of an extract of the anterior lobe produced marked hypertrophy of the cortex. Evans concluded from the evidence which he had obtained that the adrenal cortical tissue needs for its normal function some constituent of the anterior lobe of the pituitary gland. However, this experimental work does not prove that hyperfunctioning basophilic tumors of the pituitary body stimulate hyperfunction of the adrenal cortexes. The possibility that the adrenal gland is the chief offender and that pituitary disturbance is a secondary manifestation can also be entertained.

The adrenal cortical syndrome has likewise been found in cases of malignant tumor of the thymus when the latter is associated with bilateral hyperplasia of the adrenal cortex. Leyton, Turnbull and Bratton⁷⁶ reported 2 such cases. The appearance of 1 of these patients was so typical of pituitary basophilism that Cushing,^{72c} in referring to the case, ventured the opinion that further search of the pituitary body would demonstrate the presence of a basophilic adenoma. Acting on Cushing's suggestion Turnbull made serial sections of the pituitary body, and no basophilic tumor was found. A similar case was reported by me.⁷⁷ In this case the resemblance to pituitary basophilism was not so striking as in one of the cases described by Leyton, Turnbull and Bratton. Nevertheless, most of the salient features of pituitary basophilism, including osteoporosis, as described by Cushing, were present. At necropsy the chief findings were bilateral cortical hyperplasia of the adrenal glands and a thymoma. It is significant that in this case, as in a similar case in which the patient is still living and which was reported

73. Evans, H. M.: Anterior Pituitary Function, *J. A. M. A.* **101**:425 (Aug. 5) 1933.

74. Collip, J. B.; Anderson, E. M., and Thomson, D. L.: The Adrenotropic Hormone of the Anterior Pituitary Lobe, *Lancet* **2**:347 (Aug. 12) 1933. Collip, J. B.: William Henry Welch Lectures: Some Recent Advances in the Physiology of the Anterior Pituitary, *J. Mt. Sinai Hosp.* **1**:28 (May-June) 1934.

75. Houssay, B. A.: A Series of Lectures on the Hypophysis, *J. A. M. A.* **101**:1167 (Oct. 7) 1933.

76. Leyton, O.; Turnbull, H. M., and Bratton, A. B.: Primary Cancer of the Thymus with Pluriglandular Disturbance, *J. Path. & Bact.* **34**:635 (Sept.) 1931.

77. Walters, Waltman; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome: Report of Two Cases with Successful Surgical Treatment, *Proc. Staff Meet., Mayo Clin.* **9**:402 (July 3) 1934, case 2.

by Walters, Wilder and me,⁷⁸ there was a marked reduction in the concentration of blood chlorides associated with a marked increase in the carbon dioxide-combining power of the blood. This alkalosis and reduction of the blood chlorides were not the result of vomiting and diarrhea or of any of the other factors that usually produce this chemical disturbance, and consequently there is reason to suspect that it may have been due to adrenal dysfunction as well as to adrenal cortical hyperfunction. Leyton⁷⁹ recently reviewed these cases and 1 or 2 others and pointed out that the syndrome of pituitary basophilism need not necessarily be the result of basophilic tumor of the pituitary body.

A most important case has been described by Leshner.⁶⁷ In this case all of the cardinal, and most of the occasional, symptoms and signs ascribed by Cushing to adenoma of the basophil cells of the pituitary body were present. A roentgenogram of the left kidney revealed a low position of the kidney and a calcified shadow above it. The patient was operated on by Mr. Gerald Dyke, who removed a cortical cell carcinoma of the left adrenal gland. The patient died about twelve hours after the operation. At necropsy, examination of serial sections of the pituitary body revealed a slight increase in the basophil and acidophil cells, and at one point there was a small collection of basophil cells 0.3 mm. in diameter. No significant pathologic abnormalities were found in the thyroid gland, parathyroid glands, pancreas or uterus. The ovaries were atrophic. Leshner made the following statement:

In view of the case report in this patient and one or two others of a somewhat similar kind from the literature, it must be concluded that Cushing's syndrome, complete in its entirety, may be caused by such diseases as tumor of the suprarenal cortex, and so a clinical distinction cannot always be made between these two syndromes. Every case of Cushing's syndrome should be critically examined, including an x-ray examination of the abdomen for a shadow in the renal areas and for the position of the kidneys. Whilst it is generally accepted that the anterior lobe of the pituitary elaborates one or more gonadotropic secretions, there is no reliable evidence to show that the basophile cells are responsible for this. What evidence there is, is rather against this theory.

Diagnosis.—In a case in which the disease is well developed the clinical picture is so striking that it is easy to recognize that a given patient belongs to the large group having a condition often designated as a polyglandular or multiglandular syndrome. The facies, the peculiar distribution of fat, the unusual growth of hair and the history are typical. At present, however, it may be exceedingly difficult, if not altogether impossible, to differentiate with any degree of certainty pitui-

78. Walters, Waltman; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome: Report of Two Cases with Successful Surgical Treatment, Proc. Staff Meet., Mayo Clin. **9**:400 (July 3) 1934, case 1.

79. Leyton, Otto: Multiglandular Disease (Schorstein Lecture), Lancet **1**:1221 (June 9) 1934.

tary basophilism, hyperfunctioning adrenal cortical tumor, bilateral adrenal cortical hyperplasia with or without thymoma and arrhenoblastoma of the ovary. Laboratory studies thus far have yielded no constant diagnostic feature. Roentgenographic studies of the head and determination of the fields of vision may be of little value because basophilic tumors of the pituitary body are frequently so small that they can be demonstrated only at necropsy after the pituitary body is examined microscopically by serial section. In cases of pituitary basophilism obesity is confined largely to the face, neck and trunk while the extremities are spared. This peculiar distribution of fat gives the patient the distinctive habitus sometimes known as the buffalo type of obesity. In patients with the adrenal cortical syndrome the same habitus may occur, although in my experience it occurs more frequently in persons with pituitary basophilism. Hirsutism and obesity may be comparatively slight in patients with adrenal cortical syndrome. Osteoporosis is common to both diseases. Pituitary basophilism is generally a slowly progressive disease, and by the time the patient consults the physician most of the characteristic symptoms and findings are present. As I have mentioned before, the adrenal cortical syndrome may appear with considerable rapidity, and in those cases in which the onset and progress of the disease are slow and the findings closely approximate those of pituitary basophilism, localizing evidence of an adrenal tumor is likely to be present. It is my impression from a study of the cases which have been reported and of those which I have seen that pituitary basophilism is more likely to occur in its classic form, whereas marked variations in the symptoms and signs of the adrenal cortical syndrome are encountered frequently.

It is possible that this variation in symptoms which occurs in cases of adrenal tumor may depend on the degree of maturity and differentiation of the cells which comprise the tumor.

Frank⁸⁰ has recently suggested a test for functional cortical adrenal tumors. In 1 case in which there was a large carcinoma of the adrenal cortex repeated examinations of the urine for hormones over a period of four weeks revealed that large amounts of the female sex hormones were secreted. Unverified cases of pituitary basophilism were similarly examined with negative results. It is to be hoped that further studies of this type will be made and that a differential diagnostic test can be developed. From what has been said it is obvious that there is a most urgent need for a method which will differentiate the various types of endocrine disorders capable of producing the syndrome. It is well to remember that in many cases

80. Frank, R. T.: A Suggested Test for Functional Cortical Adrenal Tumor, *Proc. Soc. Exper. Biol. & Med.* **31**:1204, 1934.

the cortical adrenal tumor is frightfully malignant. If surgical intervention is to have value in such cases it must be done early. The treatment of patients with pituitary basophilism at present is not particularly satisfactory. Roentgen therapy has in some instances resulted in retrogression of the symptoms. Much valuable time can be lost by prolonged courses of roentgen therapy to the pituitary body when the disease might have been cured by removal of an adrenal tumor. In many instances of adrenal tumor the distortion of the calices in the pyelogram will make the diagnosis, although it is important to remember that the absence of positive findings in the pyelogram does not necessarily preclude the existence of a cortical tumor.

Pathologic Physiology.—Experimental cortical hyperadrenalism has never been produced. In this respect the adrenal cortex appears to be unique in the endocrine system. Doses of the hormone which are greatly in excess of physiologic needs, when administered to normal or adrenalectomized animals, result in no untoward symptoms or metabolic changes. Attempts have been made by Simpson and his associates,⁸¹ by Howard and Grollman⁸² and by Kroc and Martin⁸³ to demonstrate an influence of potent cortical extracts on the sexual and other endocrine organs of animals. To my knowledge no such attempts have been made on human subjects. It is of some significance that Kincov, Zillessen and Rowntree⁸⁴ used enormous doses of the cortical hormone for a short time in the treatment of patients with Addison's disease. They were unable to observe any harmful effects or untoward symptoms. A consideration of the available evidence leads one to believe that it is highly improbable that the symptoms of the suprarenal cortical syndrome are the result of an excessive production of the substance now known as the cortical hormone. At this point it is difficult to refrain from asking the question: By what, then, are the symptoms caused if they are not the result of excessive amounts of the cortical hormone? Two answers immediately suggest themselves: (1) the presence of another hormone as yet undiscovered in the gland, and (2) the production of an abnormal hormone. According to Kendall, the latter possibility could

81. Simpson, S. L.; Kohn-Speyer, A., and Korenchevsky, V.: The Adrenal Cortex and Sex: Influence of Cortical Extract on Normal and Castrated Rats, *Lancet* **2**:1194 (Nov. 25) 1933.

82. Howard, Evelyn, and Grollman, Arthur: The Effect of Extracts of the Adrenal Cortex on Growth and Reproductive System of Normal Rats with Particular Reference to Intersexuality, *Am. J. Physiol.* **107**:480 (Feb.) 1934.

83. Kroc, R. L., and Martin, S. J.: The Relation of Bilateral Suprarenal-ectomy and Subsequent Extract Therapy on the Body Weight and Oestral Cycle of the Albino Rat, *Am. J. Physiol.* **108**:438 (May) 1934.

84. Kincov, Jacob; Zillessen, F. O., and Rowntree, L. G.: Studies of the Adrenal Glands in Health and Disease: II. Effects of an Excess of Cortical Hormone in Addison's Disease, *Endocrinology* **18**:361 (May-June) 1934.

easily be true from the chemical point of view. This question, nevertheless, remains unanswered, and speculation is of no value except as it stimulates further investigation.

Surgical Treatment of the Adrenal Cortical Syndrome.—It is encouraging that more and more cases of successful removal of adrenal cortical tumors are being reported. Examples have been reported by Walters and his associates,⁸⁵ Collett,⁸⁸ Hicks,⁶⁸ Kolodny⁶⁹ and others. In the past the mortality following surgical intervention has been exceedingly high. This is partly because surgical technic had not developed to its present nicety and partly because in the presence of a tumor of one adrenal gland the other gland may be absent or atrophic. Even when normal the other gland apparently may temporarily cease to function after operation. Following surgical procedure it is advisable to observe the patient carefully for acute adrenal insufficiency, and if this develops to administer promptly the cortical hormone and saline solution.

HYPERFUNCTIONING MEDULLARY TUMORS

Hyperfunctioning tumors composed of primitive or adult medullary cells continue to excite medical and surgical interest. These tumors cause either continuous hypertension or attacks of paroxysmal hypertension probably as the result of an overproduction of epinephrine. The attacks are frequently associated with evidences of instability of the sympathetic nervous system, such as tachycardia, vasoconstriction followed by vasodilatation, emotional instability and other similar phenomena. C. H. Mayo⁸⁶ was the first to remove such a tumor successfully. Since then many similar cases have been reported, notably by Pincoffs and Shipley⁸⁷ and Porter and Porter.⁸⁸ The literature on this subject has recently been fully reviewed by Hick⁸⁹ and by Belt and Powell.⁹⁰ The last named authors summarized the data for 60 cases, reports of which had been published up to that time. Since then addi-

85. Walters, Waltman; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome with Presentation of Ten Cases, *Ann. Surg.* **100**:670 (Oct.) 1934.

86. Mayo, C. H.: Paroxysmal Hypertension with Tumor of Retroperitoneal Nerve: Report of a Case, *J. A. M. A.* **89**:1047 (Sept. 24) 1927.

87. Shipley, A. M.: Paroxysmal Hypertension Associated with Tumor of the Suprarenal, *Ann. Surg.* **90**:742 (Oct.) 1929.

88. Porter, M. F., and Porter, M. F., Jr.: Report of a Case of Paroxysmal Hypertension Cured by Removal of an Adrenal Tumor, *Surg., Gynec. & Obst.* **50**:160 (Jan.) 1930.

89. Hick, F. K.: A Suprarenalin-Producing Pheochromocytoma of Suprarenal Gland, *Arch. Path.* **15**:665 (May) 1933.

90. Belt, A. E., and Powell, T. O.: Clinical Manifestations of the Chromaffin Cell Tumors Arising from the Suprarenal Medulla: Suprarenal Sympathetic Syndrome, *Surg., Gynec. & Obst.* **59**:9 (July) 1934.

tional cases have been reported by Eckardt,⁹¹ Kalk,⁹² Bauer and Leriche⁹³ and others. One case, in which the patient was a child of 14 years of age, was reported by Ernould and Picard.⁹⁴ In this case the tumor was malignant, and metastasis was found in the skull. Hypertension was present. The diagnosis of hyperfunctioning medullary adrenal tumor is often difficult. The blood pressure may be normal between paroxysms, and unless the patient is observed during an attack hypertension will not be noted. In cases in which the blood pressure remains continuously elevated the symptoms may not be sufficiently distinctive, and the patient may give the impression of having ordinary severe essential hypertension. Bauer and Leriche⁹⁵ emphasized the diagnostic importance of the parallel ascent of the curves of blood pressure and blood sugar.

OPERATION ON THE ADRENAL GLANDS

A discussion of the adrenal glands would be incomplete without calling attention to the work which has been done in the field of surgery for diseases not ordinarily considered the result of disturbances of the adrenal glands. Crile⁹⁶ has recently summarized the results of 350 operations which he performed on patients with such disorders. In 53 cases adrenalectomy was done and in 297 cases denervations. Beneficial results or cure was reported in cases of neurocirculatory asthenia uncomplicated by the presence of psychosis and in cases of peptic ulcer, recurring hyperthyroidism, diabetes, epilepsy and polyglandular syndromes. Results in cases of confirmed hypertension were disappointing. Crile based his surgical procedure on the theory that the human species pays the penalty for civilization by being subject to a group of kinetic diseases in which there is a continued or intermittent widespread stimulation of the neuroglandular system. The validity of his theory is yet to be confirmed.

91. Eckardt, Friedrich: Ueber Nebennierenmarkgeschwülste im Kindesalter, *Monatschr. f. Kinderh.* **61**:127 (Nov. 27) 1934.

92. Kalk, Heinz: Paroxysmale Hypertension, Blutdruckkrisen und Tumor des Nebennierenmarkes, *Klin. Wchnschr.* **13**:613 (April 28) 1934.

93. Bauer, Julius, and Leriche, René: Zur Klinik und Therapie des Paraganglions, adrenalogene Hochdruckkrisen, *Wien. klin. Wchnschr.* **47**:1224 (Oct. 12) 1934.

94. Ernould, H., and Picard, E.: Un cas de sympathome sympathogénique avec hypertension artérielle paroxystique, *Rev. belge sc. méd.* **6**:223, (March) 1934.

95. Bauer, Julius, and Leriche, René: Contribution clinique et thérapeutique à l'étude des paragangliomes et des crises d'hypertension adrénalinique, *Presse méd.* **42**:1385 (Sept. 5) 1934.

96. Crile, George: Pathologic Physiology of the Neuroglandular System, *Am. J. M. Sc.* **189**:276 (Feb.) 1935; Indications and Contra-Indications for Denervation of the Adrenal Gland, *Ann. Surg.* **100**:667 (Oct.) 1934.

Regardless of the theory underlying the procedure, the results are exceedingly interesting and warrant careful consideration.

DeCourcy and his associates⁹⁷ performed subtotal bilateral adrenalectomy for essential hypertension, which they designated as hyper-suprarenalism. The basis for attacking the adrenal glands in cases of hypertension rests on the theory which has yet to be established that the cause of essential hypertension lies in the adrenal glands. DeCourcy's operation consists in the removal of about two thirds of the adrenal gland, in two stages. He gave the results in 6 cases, in 2 of which cortical tumors were present. It is impossible at present to evaluate DeCourcy's results. Further observation of these patients over an extended period is necessary.

It is interesting to note that attempts have been made to cure patients with Addison's disease by the transplantation of adrenal cortex. Beer and Oppenheimer⁹⁸ reported the results in 2 such cases. The first patient obtained some temporary improvement. The second patient obtained great improvement following transplantation, so that it was thought advisable to repeat the procedure several weeks later. The patient's condition improved so strikingly that the authors believed it justifiable to assume that the patient was suffering from Addison's disease and that the transplant "took." It seems likely that further developments in this field of surgery can be expected. The method developed by Stone and his collaborators⁹⁹ in transplanting thyroid and parathyroid glands might be applicable to the adrenal glands. According to this method, small fragments of the gland or a growing culture of the gland is transplanted after a period of growth in an artificial medium containing the body fluids of the host.

SUMMARY AND CONCLUSIONS

An attempt has been made to review the pertinent literature on the adrenal glands. Considerable difficulty was encountered in the selection of the material to be presented. The applicability of this material to clinical medicine was the criterion generally used in the selection which was made. Furthermore, much of the literature is not only controversial but difficult to evaluate. In such cases, I have attempted to approach the matter with an impartial and unbiased mind. If, unwittingly, my own personal feelings have crept in, I wish to apologize.

97. DeCourcy, J. L.; DeCourcy, Carroll, and Thuss, Otto: Subtotal, Bilateral Suprarenalectomy for Hypersuprarenalism (Essential Hypertension), *J. A. M. A.* **102**:1118 (April 7) 1934.

98. Beer, Edwin, and Oppenheimer, B. S.: Transplantation of the Adrenal Cortex for Addison's Disease, *Ann. Surg.* **100**:689 (Oct.) 1934.

99. Stone, H. B.; Owings, J. C., and Gey, G. O.: Transplantation of Living Grafts of Thyroid and Parathyroid Glands, *Ann. Surg.* **100**:613 (Oct.) 1934.

NOTE.—Since this article was submitted for publication, additional evidence showing the intimate relationship between sodium metabolism and the function of the adrenal cortex has been presented. Harrop and his associates¹⁰⁰ have been able to maintain the lives of adrenalectomized dogs over periods of five months solely by the administration of sodium chloride and sodium bicarbonate. These animals received no preparation of the adrenal glands. Both sodium chloride and sodium bicarbonate were necessary to maintain life. These investigators were led to try the combination of the two salts because of the observation that when sodium chloride alone was given to adrenalectomized animals sodium ions were lost from the body more rapidly than chlorine ions. This fact suggested the use of sodium salts other than sodium chloride. Allers and Kendall¹⁰¹ have confirmed the observation of Harrop and his associates. They used two dogs which had been kept alive for several months by the administration of the cortical hormone. Administration of the hormone was discontinued, and the animals were placed on a diet containing sodium citrate and sodium chloride. To make certain that the intake of sodium chloride was distributed over the entire day, a 0.7 per cent solution of the sodium chloride was used as drinking water. This combination of sodium chloride and sodium citrate in the diet was continued for eighty-four days with one dog and one hundred and fifteen days with another. At the end of this time the animals were in excellent condition and had gained weight, and the chemical constituents of the blood were entirely normal. Both animals were extremely sensitive to withdrawal of either sodium chloride or sodium citrate.

It would appear from the experiments cited that in dogs, at least, the cortical hormone is not essential to life provided the electrolyte pattern of the blood is kept normal. Excellent reviews of the relationship of the metabolism of sodium to the adrenal cortex may be found in two articles recently published by Loeb and his associates.¹⁰²

100. Harrop, G. A.; Soffer, L. J.; Nicholson, W. M., and Strauss, Margaret: Studies on the Suprarenal Cortex: IV. The Effect of Sodium Salts in Sustaining the Suprarenalectomized Dog, *J. Exper. Med.* **61**:389 (June 1) 1935.

101. Allers, W. D.: The Influence of Diet and Mineral Metabolism on Dogs After Suprarenalectomy, *Proc. Staff Meet., Mayo Clin.*, to be published. Kendall, E. C., in discussion on Allers.

102. Loeb, R. F.; Atchley, D. W., and Stahl, Jules: The Rôle of Sodium in Adrenal Insufficiency, *J. A. M. A.* **104**:2149 (June 15) 1935. Loeb, R. F.: Glandular Physiology and Therapy: The Adrenal Cortex, *ibid.* **104**:2177 (June 15) 1935.

DISEASE OF THE THYROID GLAND

AN INTERPRETATIVE REVIEW OF PROGRESS TOWARD SOLUTION OF THE PROBLEM

WALTER M. BOOTHBY, M.D.

Associate Professor of Medicine, Mayo Foundation, University of Minnesota, and
Head of Section of Clinical Metabolism, Mayo Clinic
ROCHESTER, MINN.

SURGICAL CONSIDERATIONS

Review of Progress in the Knowledge of Disease of the Thyroid.—Billroth in 1869 had performed partial thyroidectomy for goiter in 20 cases, with 8 deaths (40 per cent), and he stated: "To him who has had little practice in these operations it can easily happen that he removes the entire half of the gland instead of merely the tumor (enucleation) whereby the operation becomes very complicated and most dangerous." Most of the deaths were due to infection and only 1 to collapse (hemorrhage?).

The present review is concerned chiefly with those developments in surgical technic, clinical skill, therapeutic and preventive measures and scientific investigation which have greatly reduced the morbidity and the mortality in all types of disease of the thyroid.* As the most

* In this paper the term exophthalmic goiter has been used by preference except when the authors quoted made use of the designation Basedow's disease. In the older articles most authors included under these terms cases of adenomatous goiter with hyperthyroidism, which in turn included cases of so-called *Jod-Basedow*. In the more recent articles many authors have accepted the distinction, in accordance with the differentiation by Plummer, of adenomatous goiter with hyperthyroidism as a separate clinical entity apart from true exophthalmic goiter (true Basedow's disease). To distinguish between these two clinical conditions the continental writers usually follow the nomenclature of Aschoff, which is similar to that of Wegelin (school of Langerhans), and designate them, respectively, as *struma adenomatosa basedowificata* and *struma diffusa parenchymatosa basedowiana* (Basedow's disease). The unmodified term hyperthyroidism is used to include both the hyperthyroidism associated with adenomatous goiter and true exophthalmic goiter.

The terms endemic goiter and simple goiter are used by many writers as synonymous and include the colloid and adenomatous types (with or without degenerative changes). As endemic goiter in a considerable number of persons produces hyperthyroidism late in life (adenomatous goiter with hyperthyroidism), I prefer to use the adjective endemic instead of simple because the latter is often used to exclude hyperthyroidism, and although endemic goiter is not an ideal term its use should not be confusing. As will be seen from this review, the division of goiters into two great groups—endemic and exophthalmic—probably rests on a definite etiologic basis. However, in quoting other authors who may or may not agree with this implication I have used their own terminology.

striking recent advance has been in the reduction of mortality in exophthalmic goiter, I shall first trace the developments that have caused a progressive decrease in the surgical mortality in this disease to around 1 per cent in many large clinics where operation on the thyroid is extensively carried out and to even less than that figure in a few clinics.

That this result is not yet universal is indicated by the following reports: Labbé, one of the most noted of the French clinicians, in a special address in conjunction with Azerad to the French Surgical Society in January 1931,¹⁸¹ stated that the surgical mortality rate among patients for whom he had recommended operation for true and typical Basedow's disease was greater than 25 per cent. Duval and Welti took exception to this figure as representative of French surgery, as did also Sauvé, who maintained that it was 5.1 per cent. In a reply Labbé¹⁸² implied that diagnostic criteria would greatly influence the surgical mortality. At the German surgical congress in March 1931, under the chairmanship of von Schmieden, an entire afternoon was devoted to a discussion of the treatment of Basedow's disease. The special papers by Schneider,³⁰⁶ Bürkle-de la Camp and others are notable for their frankness, and the authors²⁵⁸ pointed out the necessity, as Labbé had done, of cooperation by the surgeons with the medical clinics and laboratories in order to reduce the mortality in the disease. The surgical review was presented by Sauerbruch, who, on the basis of observations on the cases of 430 patients operated on in the various German clinics, stated that the mortality rate varied between 8 and 48 per cent in the few years before the introduction of the Plummer method (*Plummerung*, as many German writers call it) of preoperative treatment with iodine, and that subsequent to its more or less general use the mortality rate had been reduced, on the basis of observations on 1,049 cases, to between 0 and 27 per cent. In Sweden, according to Engel, only 205 patients were operated on for the disease in Holmgren's clinic between 1913 and 1930, and 24.7 per cent of them died; although apparently not all these deaths were the immediate result of surgical procedure, the immediate surgical mortality must have been high, since following the introduction of the Plummer method it was reduced to 2.2 per cent in Troell's clinic and to 4.9 per cent in Petré's clinic. In England the mortality, in general, was high, as was indicated by the statistics of Wallace and Wevill (1933) for the Edinburgh Royal Infirmary of 12.3 per cent in 285 cases during the preceding ten years; however, Romanis, in his last 900 cases, had a mortality of 2.5 per cent, but it is not clear when he began to use iodine. In Vienna, Starlinger and Brücke reported for the years 1911 to 1930 in von Eiselsberg's clinic that 290 patients with true Basedow's disease were operated on, with an immediate mortality of 7 per cent. In this country, the report of Maes and his collaborators (1934) indicates that the surgical mortality in cases of exophthalmic

goiter in a general hospital situated in a district where thyroid disease is comparatively rare may be high. Under such conditions, with several surgeons sharing the small number of cases, he reported 19 deaths in a series of 275 cases of goiter, probably only about half of which were of the exophthalmic type. This is a mortality rate, as he pointed out, from seven to fourteen times as high as was reported from clinics where the disease is not rare, where the individual surgeons have wide experience and where there is complete cooperation with the medical and laboratory services.

I shall attempt to trace as briefly as possible the development of knowledge which has led to the successful surgical treatment of exophthalmic goiter referred to in the second paragraph. It is a complicated but fascinating story and embraces many fields of endeavor.

Goiter, because of its prominence, must have been known and referred to in the oldest medical writings. According to Garrison, Actius of Amida, who lived in the era of Justinian I (527-560), wrote an interesting chapter on goiter. Roger of Palermo in his "Practica," which was written about 1170 and was the chief textbook at the School of Salerno, prescribed ashes of sponge and seaweed (rich in iodine) for the treatment of goiter or scrofula. Paracelsus (1493-1541) was the first to establish a correlation between cretinism and endemic goiter. The use of iodine, as such, in the treatment of goiter was first studied and recommended by Coindet in 1820. The syndrome now recognized as hyperthyroidism usually associated with exophthalmos was described by Parry in 1786, by Flajani in 1800, by Graves in 1835 and by von Basedow in 1840. The syndrome of hypothyroidism, myxedema, was first noted by Curling in 1850 and was more accurately described by Gull in 1873 and by Ord in 1878. Schiff in 1884 pointed out that in dogs the fatal result which followed complete thyroidectomy could be avoided by the previous transplantation of thyroid tissue. In 1890 Horsley, having produced artificial myxedema in monkeys (1884), proposed implantation of thyroid tissue as a method of treatment. Apparently Bettencourt and Serrano were the first to try the procedure on a patient, but only temporary benefit was obtained, probably, as they thought, owing to destruction and absorption of the implant. This led to the use of a glycerin extract of thyroid tissue by Murray in 1891, which he injected subcutaneously. In June 1892 Fox reported having given orally a thyroid extract, and MacKenzie, in July of the same year, reported the administration of fresh thyroid gland.

"The Operative Story of Goiter" up to 1883, which includes Mikulicz' major contribution in 1886, was fully described with complete references and quotations by Halsted¹²⁵ (1920) in his interesting monograph of this title. Halsted was chiefly concerned in tracing the development of surgical technic as exemplified in surgical procedure on

the thyroid gland, from the oldest known operation for goiter through Billroth's ³⁴⁷ preantiseptic and postantiseptic era, Kocher's early work and the proof by Mikulicz that partial thyroidectomy through the tissue of the gland is possible to the final bloodless technic developed to such a high level of excellency by Halsted himself.

Kocher of Bern performed his first operation on the thyroid in 1872, and in 1874 ¹⁶³ he reported 13 thyroidectomies with 2 deaths. Complete removal of the thyroid gland was performed in 2 of these cases, and although 70 operations for goiter had been reported before 1850 and 146 up to 1877, these 2 extirpations of the thyroid gland reported by Kocher are probably the first successful operations of this type. He quoted Billroth as making the statement that it was not yet known whether or not a human being could survive the operation. Reverdin in 1882 made a preliminary report ²⁹⁴ of a peculiar condition following complete removal of the thyroid gland, which in the following year was more clearly described as cachexia strumipriva by Kocher (1882 and 1883) on the basis of 101 thyroidectomies with 13 deaths (12.8 per cent). Of these, 34 were complete thyroidectomies, with 3 deaths. Reverdin and Reverdin ²⁹⁵ in the same year gave a similar detailed description of the late effects produced by complete thyroidectomy in 22 cases. In some of Kocher's cases of cachexia strumipriva the condition was pure post-operative myxedema, while in others (as is now known) there was evidence of simultaneous parathyroid insufficiency (tetany). The correlation between the symptoms of thyroid insufficiency in cases of cachexia strumipriva and Gull's disease (myxedema) was pointed out by Semon in discussing a case presented before the Clinical Society of London on Nov. 23, 1883. As a result, a committee of the society was appointed, and presented its classic "Report on Myxedema" in 1888.²⁹³ This should be read by every one interested in thyroid disease. Although Sandström had described the parathyroid glands in 1880, the tetanic group of symptoms sometimes occurring in cases of cachexia strumipriva and experimental thyroidectomy (which included parathyroidectomy) was unexplained until the physiologic importance of these symptoms was clarified by the studies of Gley in 1891 (references 101 to 104), Gley and Nicolas ¹⁰⁶, and Vassale and Generali (references 331 to 333) in 1896. Halsted (references 120 to 122) and Halsted and Evans in subsequent reports added a great deal to the knowledge of practical methods of avoiding injury to the parathyroid glands as well as to a clearer understanding of their physiology.

Rehn ²⁸⁸ in 1880 performed the first thyroidectomy on a patient with Basedow's disease, and in 1883 he presented the patient before the Medical Society of Frankfort; the patient had remained completely cured during the three years following operation. In 1900 Rehn ²⁸⁹ was able to collect, by personal communication, records of thyroid-

ectomy on 177 patients with Basedow's disease from 37 different surgeons, with a mortality of 13.5 per cent; he collected reports of an additional 114 instances from the literature, in which there was a mortality rate of 11.4 per cent. He pointed out that if only the severe cases were considered (95) the mortality would be 22 per cent.

Following his extensive report on the results of complete thyroidectomy and recognition of the syndrome of cachexia strumipriva as myxedema, Kocher abandoned the operation of complete thyroidectomy and returned to the procedure of partial thyroidectomy, which was often simple enucleation of the goitrous tumor; in short order he reported successively the results of his first (1895),¹⁶⁷ second (1901)¹⁶⁸ and third (1906)¹⁷⁰ thousand operations. In Kocher's second thousand operations (in which were included operations for Basedow's disease, with a mortality of 8 per cent), the operative mortality was as follows: In 27 cases thyroidectomy was performed for the removal of a malignant thyroid gland, with 6 deaths; in 20, thyroidectomy was performed for strumitis, with 2 deaths; in 24, thyroidectomy was performed for morbus Basedow, with 2 deaths (8 per cent), and in 929, thyroidectomy was performed for simple goiter, with 4 deaths (0.4 per cent). In a total of 1,000 thyroidectomies of all types there were 14 deaths (1.4 per cent).

While several surgeons made early and important contributions to the development of the surgical treatment of exophthalmic goiter, during the next few years the major contributors in developing the field were Kocher in Europe and Halsted, C. H. Mayo and Crile in this country.

Albert Kocher¹⁶⁰ published in 1902 an exhaustive monograph of more than 300 pages on a complete analysis of the 59 cases of Basedow's disease (4 deaths) in which the patients had been operated on by his father. The beneficial results of operation were most gratifying: Seventy-six per cent of the patients were considered cured, 14 per cent were improved and 3.3 per cent were slightly improved; the mortality rate was 4.7 per cent. In the surgical treatment of Basedow's disease Kocher developed the principle of multiple operation, consisting of preliminary ligation followed by one or more partial thyroidectomies. Pages 197 to 199 are devoted to the discussion of the use of iodine, and it is obvious from this and from the histories of cases presented in the report that many of the patients received iodine before operation, with obvious temporary improvement, whereas others apparently were made worse by it (or became worse after its use). While microscopic examination of the thyroid glands revealed in most cases diffuse parenchymatous hypertrophy and hyperplasia, in some cases it did not, as one would anticipate in a district where goiter is endemic, and the patients in the latter group, as one today restudies these cases, were apparently

most harmed by iodine. One cannot help but regret that this distinction was not fully and completely recognized and also that these early investigators failed to distinguish the frequent sudden aggravation of symptoms in true Basedow's disease from the sudden omission of iodine from its actual beneficial effect while it was administered. In considering this and the later reports of Kocher and other surgeons who had a low mortality rate in their cases of exophthalmic goiter in contrast to the subsequent high mortality rate of from 8 to 48 per cent in the big European surgical clinics previously mentioned, compared with the recent low mortality rate reported from America after the demonstration by Plummer ²⁸¹ in 1922 and 1923 of the value of iodine in the preoperative preparation and postoperative treatment of patients, it would be of interest to know whether or not iodine unknowingly played a rôle in some of the early surgical cases reported. Sauerbruch stated at the 1931 German Surgical Congress: "The astonishingly great difference in the number of deaths . . . cannot be attributed to variation in operative skill but must be attributed to the difference in the preoperative preparation." In light of this it would be interesting to know whether or not at the time of Kocher's lowest mortality rate iodine in some form or other was being extensively used in the University Hospital of Bern, either as medication or as an antiseptic, especially in view of the fact that Albert Kocher ¹⁶² in 1910 made an extensive study of the difference in the pathologic findings and the iodine content of glands with Basedow's disease, depending on previous iodine medication. Thompson, Brailey and Thompson ³²¹ have shown that 1 drop of compound solution of iodine U. S. P. daily will in many cases be sufficient to lower the basal metabolic rate and in some instances prevent the fatal crisis of exophthalmic goiter. Even if no iodine was administered to the patient the "odor" of iodine, if it was being used extensively in the hospital and was continuously inhaled by the patient, might be sufficient to have an appreciable effect. Lerman and Means have shown that the inhalation of ethyl iodide is as efficacious as the ingestion of potassium iodide. Furthermore, Aschoff's pupil, Uffenorde, in beautifully conducted experiments has shown that the air at Bad Salzungen in Thuringia (the spray from the spring enriching the air with iodine) prevents the development of endemic goiter in rats which at Freiburg develops in rats under otherwise identical conditions. The following observation by Ochsner (1905) suggests that some comparable change in technic may have been made by others but without recognition of the significance:

I have had a peculiar experience in regard to use of iodoform gauze in these cases. Some years ago Kocher made the statement that in thyroidectomy no antiseptic solution should be used. Before that time I had tamponed the raw surface with iodoform gauze—and the patients went on to recovery without any disturbance. Then when this statement was made I simply inserted a small drain

tube and used no iodoform gauze, but the patients did not do so well. That being the only difference in treatment, I went back to the use of iodoform gauze and my patients did better again.

In fact, an excellent example of the unsuspected effect of iodine was the experience of Halsted¹¹⁶ in the production in dogs of compensatory hypertrophy of the remnant of thyroid tissue after nearly complete thyroidectomy, which was first observed by him in 1888 and commented on by Welch. Halsted did not report these experiments in detail until 1896;¹¹⁷ in the second series he reported, in 1914,¹²⁴ he was disturbed because he was unable to duplicate the compensatory hypertrophy obtained in the first series. In some of the later operations iodine was used as a disinfectant of the skin although not in all instances; however, iodine was freely used about the laboratory, and the vapor was therefore prevalent. Consequently the presumption is, as was suggested by Marine in a letter to Halsted, that iodine was the cause of his conflicting results. Marine and Lenhart demonstrated as early as 1909 that iodine will prevent hyperplasia of the thyroid. It will be remembered by all those familiar with the details of the surgical technic that about this time iodine was extensively used as a wound disinfectant and that at the end of the operation the entire wound was frequently swabbed with a solution of iodine.

From this slight digression one returns to a consideration of the development of thyroid surgery. Kocher reported in 1906 his third thousand thyroidectomies for all types of goiter; there were only 7 deaths—a remarkably low mortality. Kocher's brilliant results naturally stimulated thyroid surgery throughout Europe, but no one was able to report such consistently low mortality rates, and only a few surgeons had the advantage of having a large amount of endemic goiter material on which to develop technic and experience. In this respect C. H. Mayo has been fortunate, in that Rochester, Minn., is situated in the center of the American goiter belt. Mayo reported early in 1904²⁴⁵ the cases of 110 patients who were operated on for goiter of all kinds, and by the latter part of that year²⁴⁶ he had operated on 40 patients with exophthalmic goiter, with 6 deaths. Halsted¹¹⁸ reported in 1905 that he had operated on 46 patients with mild symptoms of exophthalmic goiter, with only 1 death, and in 1907¹¹⁹ he reported 90 cases with only 2 deaths.* At the meeting of the Southern Surgical and Gynecological Society in December 1908 Mayo²⁴⁷ reported 1,000 operations on 979 patients (of whom 574 had a simple goiter), with 4 deaths (0.7 per cent), and on 405 patients with severe hyperthyroidism, with 19 deaths (4.7 per cent); 4 of the last mentioned were among his first 16 patients.

* One wonders whether iodine could have played a rôle in Halsted's clinical results as it did in his experimental work just referred to. Also, in Baltimore, much sea food is eaten, which is rich in iodine.

Crile in 1908⁶⁶ reported 225 operations on the thyroid gland; 142 of these were for benign tumor or hypertrophy with only 1 death, and 28 were on patients with exophthalmic goiter, with 4 deaths. These operations were performed prior to the introduction of his new technic of "stealing" the gland; in 13 cases there were no deaths after the introduction of that technic. This report of Crile's, together with his subsequent reports⁶⁷ on the advantages to be gained not only from "stealing" the gland, but also from his insistence on the careful handling of the tissues, as later embodied in his principle of "anoci-association," materially helped to reduce the operative mortality in exophthalmic goiter as well as in other fields of surgery.

The first really large series of patients operated on for hyperthyroidism was that reported by Mayo²⁴⁸ in December 1910; he had then operated on 1,100 patients for hyperthyroidism, with the following mortality rates: following ligation, 3.7 per cent, and following thyroidectomy, 3.9 per cent.

In 1910 Kocher¹⁷² reported 4,629 thyroidectomies for all types of thyroid disease. During this time he had performed 721 operations on 537 patients with Basedow's disease, with 17 deaths (3.2 per cent), of which 5 followed ligation. In his last 629 operations Kocher performed 462 on patients without symptoms of Basedow's disease, with no deaths, and 167 on patients with symptoms of Basedow's disease, with 4 deaths (2.3 per cent), although there were 5 additional deaths while patients were being prepared in the operating room, which, if considered due to the surgical procedure, would make the total mortality 5.4 per cent. The next year (1911 and 1912) he regrouped these and his additional cases on the basis of the number of operations, which gave a mortality rate of 2.3 per cent for 876 operations for Basedow's disease.

A consideration of the first phase in the development of the surgical treatment of exophthalmic goiter can be ended with the report of C. H. Mayo in 1914; during the twenty-six years ending July 1, 1914, he and his associates at the Mayo Clinic had performed 6,960 operations on the thyroid gland, of which 3,327 were for hyperthyroidism. The mortality rate in hyperthyroidism, on the basis of the number of operations, varied between 1 and 3 per cent, and as many as 278 consecutive operations had been performed without a death.

During this first phase many other contributions appeared which I am unable to include because of the limitation of space. Some of them contained reports of equally good results, although based on a much smaller number of cases; for example, an additional small series of 39 cases was reported by Halsted¹²³ in 1913, with no deaths. Although these papers contributed many important details to the general surgical

knowledge, they did not materially alter the general trend indicated by those specifically mentioned.

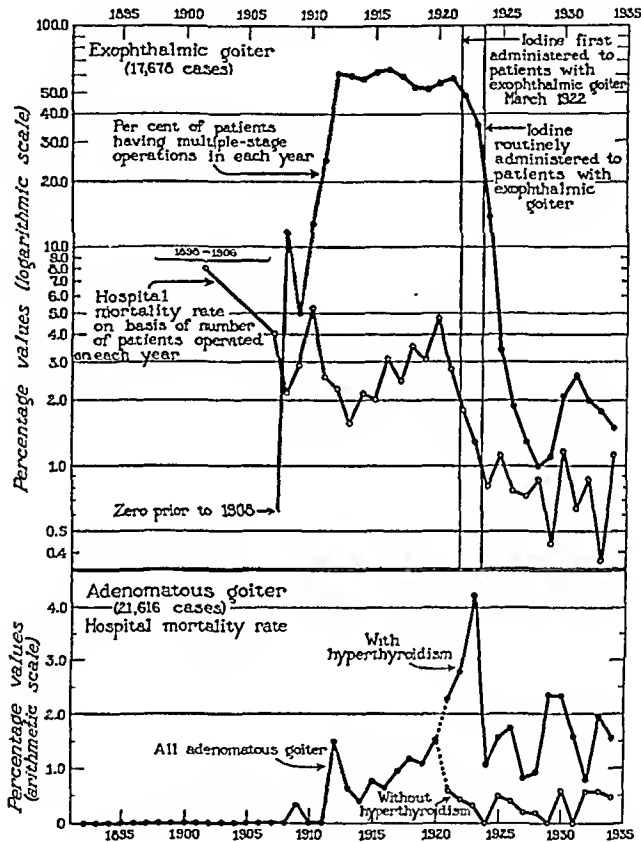
During the following ten years, between 1913 and 1923, which may be considered the second phase, the surgical treatment of exophthalmic goiter remained essentially stationary. In Europe the war stopped further progress, and even in this country it materially slowed down further developments with a few exceptions. Crile⁶⁸ continued to improve his technic of "stealing" the gland and developed his theory of the "kinetic drive." In 1922⁷⁵ he reported a mortality of 1.4 per cent for his last 1,783 thyroidectomies, of which 1,022 were for exophthalmic goiter.

In the same year Pemberton²⁷⁵ reported the following statistics for the Mayo Clinic from July 1, 1920, to June 30, 1921: One thousand nine hundred and fifty-four patients were operated on for goiter of all types (excluding cancer), with 35 deaths, giving a mortality of 1.8 per cent; 996 of these patients were operated on for simple goiter, with 8 deaths, making a mortality of 0.8 per cent; 281 were operated on for hyperfunctioning adenomatous goiter, with 4 deaths, making a mortality of 1.4 per cent, and 677 were operated on for exophthalmic goiter, with 23 deaths, making a mortality of 3.4 per cent, with a total of 1,234 operations, giving a mortality rate in cases of exophthalmic goiter of 1.9 per cent on the basis of the number of operations.

The third period of operation for exophthalmic goiter began in 1922. The preliminary report of Plummer, to the effect that the administration of iodine will prevent the crisis which causes death in exophthalmic goiter, was made at the meeting of the Association of American Physicians in May 1923. Under his direction iodine in the form of the compound solution (U. S. P.) was first administered early in March 1922 to patients with exophthalmic goiter in doses of 10 drops (0.6 cc.) three times a day as soon as they came under observation at the clinic, and the administration of iodine was continued until a considerable time after operation. The previous use of iodine and the reasons leading to Plummer's trial of it in a large series of cases will be discussed in a subsequent section of this review. I shall now merely present the evidence of its value in the treatment of patients with this disease by its effect "(1) in increasing the operability of the patient, (2) in decreasing the number of operations necessary, (3) in reducing or almost eliminating surgical mortality, (4) in decreasing and almost eliminating the medical mortality and shifting these formerly 'hopeless' into operable cases. (5) in almost completely transforming that group of postoperative patients who had some residual symptoms into complete cures, and (6) in completely controlling a large portion of recurrences."

Pemberton²⁷⁶ and Pemberton and Haines²⁷⁷ recently reported the surgical mortality in 27,057 cases of thyroid disease (excluding carcinoma) in which patients were operated on at the Mayo Clinic since 1918. In these papers they have given an illuminating discussion of the decrease in the mortality rate and of the increase in operability of exophthalmic goiter following the introduction of Plummer's method of the administration of iodine. Recently C. H. Mayo and Pemberton, under whose personal care a large proportion of the patients were, elaborated this study by including the cases of all patients operated on for goiter at the Mayo Clinic since the first operation for adenomatous goiter without hyperthyroidism, performed in 1892, and the first for exophthalmic goiter, performed in 1898, down to and including 1934. For the purposes of their study the records in the statistical department of the Mayo Clinic were checked and verified. Throughout the study a consistent method of recording deaths was adopted, as follows: All deaths were included which occurred in the hospital, irrespective of the duration of hospitalization, following any surgical procedure for either exophthalmic goiter or adenomatous goiter with or without hyperthyroidism, no matter what the immediate cause of death might have been (including 1 instance of suicide) and regardless of the severity of any complicating factor such as diabetes, organic cardiac disease, embolism or other complicating condition. Fifteen thousand, nine hundred and seventy-three patients were operated on for exophthalmic goiter and 21,255 for adenomatous goiter, making a total of 37,228 patients on whom 45,824 operations were performed; in addition, there were 442 patients with carcinoma of the thyroid, whose cases, however, will not be considered in this review. Beginning in 1918 the basal metabolism was determined by members of the section on clinical metabolism in many of the cases of thyroid disease, and since 1921 in practically all cases in which there was any question of hyperthyroidism; therefore, for the last seventeen years the clinician had these data to aid in making the correct differential diagnosis. With the exception of the very early years of the report, the members of the section of surgical pathology carried out histologic examination on all thyroid tissue removed, and the report was correlated with the clinical diagnosis at the end of each year by H. S. Plummer. Also, with the exception of the first few years, all the patients were seen and the condition was diagnosed in either the medical section of H. S. Plummer or that of W. A. Plummer by consultants thoroughly trained in making the correct differential diagnosis of thyroid disease. The data on the cases have been grouped according to the clinical diagnosis. Plummer's classification of goiter was used, and the cases were separated into two large groups: (1) exophthalmic goiter and (2) adenomatous goiter.

Space prevents an attempt to give the analysis of this immense amount of material by each year; therefore, I reproduce only the summarized tables in large yearly groups (tables 1 and 2 and a chart giving the yearly results). In the tables it will be noted that two subdivisions have been made on the basis of (1) the number of individual patients operated on each year (that is, a patient is counted once each year in which he or she was operated on, no matter how many operations were performed on him or her that year) and (2) the total number of opera-



Decrease in mortality with operation for goiter following introduction of the administration of iodine (C. H. Mayo and Pemberton, 1935).

tions performed (that is, the operation is considered as the unit). Every death in the hospital has been included, and the mortality rate has been expressed on the basis of these two subdivisions. Additional data are given in table 1 showing the percentage of patients in each yearly group who had more than one operation. All the data are presented in graphic form in the chart for each year, except for the cases of exophthalmic goiter before 1907, which have been presented as a group, as they were too few to give the yearly figures statistical significance. It is to be hoped that members of other clinics in which a sufficiently large number of patients are treated for thyroid disease will likewise present their data in

detail, as much of value about the disease as well as about the success or failure of variations in surgical technic and in the use of iodine could thereby be obtained which would justify the time and effort needed for its compilation.

In this review I shall refer only to the most important points brought out by this study. Following the use of iodine the mortality rate for patients with exophthalmic goiter, as is shown in table 1 and in more detail in the figure, was reduced to almost one fourth of what it had been before. Impressive as this is, it does not begin to tell the whole story, and the data presented must be considered in conjunction with another factor, namely, the increase in operability resulting from the use of iodine. By the administration of iodine the patient was in most instances rendered in a safe condition within from about ten days to three weeks or occasionally longer for

TABLE 1.—*Hospital Mortality Rate for Patients with Exophthalmic Goiter and Percentage of Multiple Operations Performed**

Period	Hospital Mortality		Multiple Operations, Percentage of Patients
	Per 100 Patients	Per 100 Operations	
1898-1906.....	8.04	8.04	0
1907-1911.....	3.24	2.82	13.5
1912-1916.....	2.32	1.20	61.0
1917-1922.....	3.13	1.73	54.3
1923-1928.....	0.90	0.83	6.4
1929-1934.....	0.75	0.74	1.8

* From statistics correlated by C. H. Mayo and Pemberton (1935).

primary subtotal thyroidectomy, thus making almost entirely unnecessary the previous method of from one to four ligations followed in two to three months by subtotal thyroidectomy, even then not infrequently performed as a two-stage instead of a one-stage procedure. Not only was this a great economic saving to the patient, but it obviated completely the interim mortality—the rate of which was never exactly known, although it must have been appreciable. Likewise, the considerable number of patients who formerly came to the clinic in a cerebral or gastro-intestinal type of crisis for whom nothing could be done and who in consequence died shortly after arrival has been reduced to an insignificant figure as the result of immediate and adequate iodine therapy; nearly all these patients, as well as some others who, although they did not immediately die were too sick to be operated on, now in a few weeks become reasonably good operative risks, and it is in this group of formerly exceedingly sick patients that most of the small present-day mortality is found. The numerical importance of the increase

in operability is shown by the fact that in the eleven years before iodine was used approximately 58 per cent of the patients had multiple operations, such as ligation or the injection of hot water, and many of them had several such procedures before it was considered safe to attempt subtotal thyroidectomy, and subsequent to the use of iodine the number of patients who required multiple operations, including those for a recurrence of the disease, was reduced to an approximate average of 1.8 per cent for the last six years.

The mortality rate for patients with adenomatous goiter is given in table 2.

In the upper half of the chart is indicated the rapidity with which the necessity for multiple procedures was reduced by the use of iodine, together with the yearly surgical mortality rate in patients with exophthalmic goiter on the basis of the number of patients operated on and not

TABLE 2.—*Hospital Mortality Rate for Patients with Adenomatous Goiter**

Period	Hospital Mortality					
	All Adenomatous Goiter		With Hyperthyroidism		Without Hyperthyroidism	
	Per 100 Patients	Per 100 Operations	Per 100 Patients	Per 100 Operations	Per 100 Patients	Per 100 Operations
1892-1906.....	0.00	0.00
1907-1911.....	0.13	0.13
1912-1916.....	0.71	0.70
1917-1920.....	1.22	1.21
1921-1923.....	0.87	0.86	1.70	1.67	0.34	0.34
1929-1934.....	1.03	1.03	1.96	1.96	0.32	0.31

* From statistics correlated by C. H. Mayo and Pemberton (1935).

on the number of operations done; in the lower half are presented similarly the data for patients with adenomatous goiter and, after 1921, with the hyperthyroid and the nonhyperthyroid forms, charted separately.

While iodine played the major part in the recent reduction of the mortality rate in surgical procedure in persons with exophthalmic goiter, other factors simultaneously have played a part in this reduction. First are the innumerable refinements in surgical technic which practically obviate injury to the recurrent laryngeal nerves and to the parathyroid glands (the dangers of hemorrhage were largely overcome in Kocher's time). In addition, if pneumonia develops postoperatively or the recurrent laryngeal nerve is injured, an occurrence which favors the development of pulmonary edema and pneumonia, the harmful effects of anoxemia can almost always be controlled by the administration of oxygen by means of the oxygen chamber or the modern oxygen tent, as demonstrated by Haines and me. Even if the parathyroid glands are injured the results are no longer feared, as the condition can be

easily and completely controlled by the proper use of calcium lactate, cod liver oil and parathyroid extract, the last being rarely needed (Boothby, Boothby, Haines and Pemberton and Boothby and Waltman).

Many patients who have had exophthalmic goiter, and especially those with adenomatous goiter with hyperthyroidism, for many years have a fatigued heart with more or less decompensation which is often superimposed on an independent organic heart disease such as valvular lesions, coronary sclerosis and angina pectoris. Medical cooperation in the handling of these cases before and following operation has been emphasized by many. The dangers of the improper use of digitalis were clearly brought out by Plummer, especially with the group of older patients who have adenomatous goiter with hyperthyroidism associated with decompensation. The proper care of the patient who has diabetes associated with hyperthyroidism has been particularly studied by Wilder and in Boston by Joslin and Lahey, and they have shown that the requirement for insulin is often greatly increased when the patient is on the verge of a crisis; the sugar content of the urine and the blood following operation must be carefully followed, and the appropriate amount of insulin must be used early to prevent the superimposition of diabetic coma. Wilder has shown that as the patient with exophthalmic goiter improves with iodine therapy there is corresponding improvement in the associated diabetes, with an increase in the carbohydrate tolerance and a reduction in the requirement for insulin (references 33, 34, 36, 37, 38, 40, 41 and 46).

Mention must be made of the use of iodine in the treatment of adenomatous goiter as opposed to its use in the treatment of exophthalmic goiter. At the Mayo Clinic iodine is not given except for special purposes to a patient who has adenomatous goiter without hyperthyroidism. However, since 1923 it has been freely given, but not as a routine, to patients who have adenomatous goiter with hyperthyroidism, and no harm has been noted from such use within the week or two before operation is performed. Some of the patients are better following its administration, and some have always shown periods of improvement without its use. The mortality rate shown in the chart in cases of adenomatous goiter with hyperthyroidism is possibly slightly lower after the use of iodine than before, but the decrease is not nearly so great as in cases of exophthalmic goiter. As a matter of expediency and safety iodine is usually given to patients with adenomatous goiter with hyperthyroidism to avoid the possibility of a fatal accident consequent to an erroneous preoperative clinical diagnosis which consists in mistaking a mild case of exophthalmic goiter with an incidental adenoma in the gland for a case of adenomatous goiter with hyperthyroidism.

Crile in 1928⁶⁹ and 1929⁷⁰ reported excellent surgical results in the treatment of hyperthyroidism, and in 1930⁷¹ reported that he

and his associates had performed on Sept. 9, 1929, the twenty thousandth operation on the thyroid gland. Of such operations 5,354 were ligations and 13,814 were thyroidectomies; 10,125 of the thyroidectomies were for hyperthyroidism, 3,689 for simple goiter. Crile had one series of 982 operations without a death, if only patients less than 50 years of age are considered, and the mortality under his plan of management embraced in his principle of anoci-association, of stealing the gland and of multiple operation had been reduced to 0.5 per cent for all operations. During the last few years Crile (references 72 to 74) has been intensely interested in the rôle the adrenal glands may play in the syndrome of exophthalmic goiter, and his most recent reports have been concerned chiefly with that interesting phase of the problem of thyroid disease. The results he has already obtained are very interesting; they are, however, as yet inconclusive as to the clinical value of this method of attack.

Another wonderful record for American surgery is found in the results reported by Lahey¹⁸⁶ in 1934 (table 3). He adopted essentially

TABLE 3.—*Results in Treating Hyperthyroidism**

	Cases	Operations	Deaths	Patients, Percentage of Mortality	Operations, Percentage of Mortality
Primary hyperthyroidism (Basedow's disease)...	3,422	4,543	21	0.61	0.48
Toxic adenoma.....	876	1,032	16	1.80	1.50
Total.....	4,298	5,575	37	0.86	0.66

* Based on results reported by Lahey (1934).

the classification used by Plummer, but he did not divide his statistics in such a manner that the effect of iodine can be determined, probably because comparatively few of his patients were operated on in the pre-iodine era.

In a five year follow-up in 97 cases Lahey¹⁸⁷ found 82 patients who were perfectly well, 7 who were well after another operation and 3 who were well, but only with the constant administration of iodine. In conjunction with Hurxthal, Lahey commented at length on the postoperative end-results in 300 patients with thyrocardiac disease.

In addition to the three large series of operations on the thyroid just detailed, many smaller series with similar good mortality rates could be cited from the American surgical literature. In fact, as a result of the general use of iodine before and after operation thyroid surgery is performed satisfactorily and with a low mortality rate in nearly all surgical clinics in the American goiter belt and wherever exophthalmic goiter is prevalent. Reports during the last year in Europe, a few of which I have previously referred to, are rapidly increasing in number and show a greatly decreased mortality

rate as the members of the various European surgical and medical clinics have adopted and have become familiar with the details of the correct method of administration of iodine in cases of exophthalmic goiter.

This section of the review can best be ended with mention of the contribution to the knowledge of thyroid surgery made in England by Joll.¹⁴⁸ In a series of 702 cases of exophthalmic goiter he had a mortality rate of 2.9 per cent; however, in the earlier part of his series apparently either iodine was not used or experience was being acquired in its use, which probably explains why the mortality rate was slightly higher than in some of the series recently reported on in this country.

Results of Medical Treatment.—No very accurate statistics on the medical treatment of exophthalmic goiter are available. In 1918 McCarrison²¹⁶ collected all the available data and concluded that with rest and ordinary medical attention it may be reasonably expected that at least 50 per cent of all patients will eventually recover to the extent of being capable of fulfilling their daily duties more or less efficiently. Thus, of 3,523 patients so treated whose cases he was able to find records of in the literature, recovery was stated to have occurred in just over 50 per cent; in 39 per cent the condition had been alleviated or had become chronic, whereas death had resulted from the disease itself in 12 per cent. In fatal cases death usually occurred within a period of from six months to six years after the onset; in more than 50 per cent it occurred within eighteen months.

The most recent statistics on the nonsurgical treatment of exophthalmic goiter are in the excellent study of Eason and Wallace (1932). They divided their cases into two groups: Group 1 (1921-1926) contained 180 patients. In the follow-up replies were received as to the condition of 143 patients; of these, 120 were known to be alive, and 23 were known to have died, which is a mortality of 16.1 per cent, if it is assumed that those not heard from were alive. Ten of those who died were definitely known to have died as the result of the exophthalmic goiter. Twenty of the patients reported that they were unfit for work.

Group 2 (1927-1930) contained 135 patients. In the follow-up replies were received as to the condition of 118, of whom 114 were known to be alive and 4 to have died, which is a mortality of 3.4 per cent, again if it is assumed that those not heard from were alive. Twenty-nine of those reporting said that they were unfit for work.

With the reduction of the surgical mortality to less than 1 per cent and with that mortality occurring in large part in the severe cases of long standing, interest in roentgen therapy as a means of controlling the syndrome of exophthalmic goiter has almost entirely disappeared.

Even if all the claims made by the advocates of roentgen therapy are granted, the results are so inferior to those obtained by partial thyroidectomy in conjunction with the proper use of iodine that space need not be taken here to present the facts in detail.

IODINE THERAPY

The changeable rôle that iodine has played in the treatment of various forms of goiter must now be traced. As has been mentioned, the ancients discovered that seaweed, which is now known to contain iodine, was beneficial in the treatment of goiter. Following the report of Coindet in 1820 of its beneficial effects iodine was used extensively, and the literature of the time contained many favorable as well as unfavorable reports. It became such a popular remedy that the people, according to St. Lager (1867), carried small bottles of iodine hung around the neck like a charm. From the work of Aschoff's pupil, Uffenorde, it is now known that this practice would probably be a reasonably good prophylactic procedure. Chatin⁵⁶ (1851-1854) carried out extensive investigations of the distribution of iodine in water, in the soil, in plants, in animals and even in the air; he concluded that a lack of iodine was the cause of goiter and recommended that in districts where goiter was endemic it could be prevented by adding iodine to the water supply. His proposal was not, however, accepted by the French Academy. Since his work no systematic investigation of the distribution of iodine in water and soil was made until the recent work of McClendon (1923-1934) and, to a lesser extent, that of von Fellenberg. Gley,¹⁰⁵ according to Garrison, in 1889 demonstrated the existence of iodine in the thyroid gland and blood. Although this attracted no attention, Kocher¹⁶⁶ (1895) suggested that the normal gland probably contains iodine. E. Baumann (1895 and 1896) definitely proved this fact and separated an iodine-containing compound from the thyroid gland which he called thyro-iodin and latter iodothylin. Murray in 1891 and Fox and MacKenzie independently in 1892 had shown that thyroid extracts administered either subcutaneously or orally would control myxedema, and it was quickly demonstrated that iodothylin produced the same clinical effect. Hutchison (1896 and 1898) investigated the proteins of the thyroid gland which were first described by Bubnow in 1884. Oswald²⁷² demonstrated (1896 to 1901) that an iodine-containing thyroglobulin could be satisfactorily purified from the proteins of the thyroid gland and that it was physiologically active and therapeutically effective in myxedema. He²⁷³ demonstrated that the iodine content of the thyroglobulins obtained from persons with goiter was much lower than that of thyroglobulins obtained from the thyroid glands of animals; the iodine content was very low in the thyroglobulins obtained from persons

with exophthalmic goiter. It therefore became evident that the functional and pathologic activity of the thyroid gland is in some way connected with iodine. The rôle which iodine plays in the formation of the normal secretion of the thyroid gland was not finally cleared up until after Kendall in 1914 (1915; 1919) isolated thyroxine in crystalline form; Harington in 1926 (references 127 and 128) determined its structural formula and Harington and Barger synthesized it in 1927.

Although much was written in the older literature for and against the administration of iodine to persons who had simple goiter, no systematic study of the problem was made until Kocher¹⁶⁰ emphasized the harmful effects often produced by its uncontrolled use in the endemic goiter district of Switzerland. Under his direction an extensive clinical and chemical study was made of the problem by his son, Albert Kocher.¹⁶¹ One of the best of Theodore Kocher's articles on the use of iodine in the treatment of thyroid disease was published in 1905 as a lecture on "Die Therapie des Kropfes" in *Deutsche Klinik*.¹⁶² In this study he presented clearly the various types of goiter for which iodine can be given with safety and emphasized the harm that can result to patients with a certain type of goiter from an indiscriminate and unguided use of iodine. Kocher was very emphatic about the dangers of iodine, especially those from the injection of iodine directly into the thyroid gland. On the other hand, he remarked on the occasional brilliant results which he had observed as well as found reported in the literature following the administration of iodine to patients with Basedow's disease.

There seems to be no doubt that he saw many patients with simple endemic goiter¹⁷¹ but who had no, or only slight, constitutional symptoms of hyperthyroidism and who became worse following the use (or possibly the misuse) of iodine. The syndrome thus produced resembled that produced by an overdose of preparations of thyroid gland, which in turn resembled that of Basedow's disease. For this condition Kocher¹⁷² devised the name *Jod-Basedow*, although he recognized that it was not true Basedow's disease but a "frequent and important form of Basedow's disease which is brought about by the (improper) administration of iodine to patients with endemic goiter." In all his papers he so emphatically emphasized the dangers of the "improper" use of iodine that the members of the medical profession were led to believe that it was malpractice to give a patient with Basedow's disease iodine in any form, in spite of the reports of almost miraculous benefit which occasionally appeared in the medical literature and the cases which Kocher himself had observed. As emphasized by Means and Lerman in their paper on this subject which was read last May at the meeting of the American Medical Association, the choice of the name *Jod-*

Basedow was most unfortunate on account of the erroneous connotation therein implied that true Basedow's disease may also be caused by the administration of iodine. However, the intensive form of endemic goiter existing through, and producing its effect over, many generations, including a prenatal influence, does not occur in the United States. Therefore, in this country one must be guarded as to the judgment of the effect which iodine may produce in this type of goiter and in the various forms of cretinism which develop in such an environment.

According to Albert Kocher¹⁶⁰ (1902), the reports made by Langerhans on the pathologic changes in the thyroid gland showed in most cases diffuse parenchymatous hypertrophy, thus agreeing with Greenfield's (1893) and Lubarsch's²⁰² (1895) observations as to the characteristic pathologic changes in true Basedow's disease. However, as some cases of adenomatous goiter with hyperthyroidism (*Jod-Basedow*) are included in Kocher's series,¹⁷² there were many instances in which the pathologic changes were those usually seen in cases of endemic goiter, thus confusing the clinicopathologic correlation of Basedow's disease.

In a pathologic and chemical study of 160 thyroid glands from patients with Basedow's disease, Albert Kocher¹⁶² found in only a fifth of the glands a nodular type of goiter, whereas in four-fifths there was diffuse hypertrophy of about the same degree throughout the gland, although the intensity of hypertrophy varied in degree in different cases. He also found that the degree of hypertrophy varied with the iodine content, which in turn depended on how recently the patient had been receiving iodine.

MacCallum reported a high incidence of diffuse parenchymatous hypertrophy and hyperplasia in the thyroid glands removed by Halsted from patients with exophthalmic goiter. Wilson (1908; 1913; 1914; 1915; 1916; 1922) and MacCarty (1912; 1913; 1931) found a similar high ratio in thyroid glands removed at the Mayo Clinic when correlated with Plummer's peroperative diagnosis of exophthalmic goiter and adenomatous goiter with hyperthyroidism (at that time Plummer was noncommittal in his terminology and used the terms toxic hyperplastic and toxic nonhyperplastic, respectively). On the other hand, Marine and Lenhart (1911) studied the thyroid glands removed at Lakeside Hospital (Crile's surgical and Hoover's medical service) and found no consistent pathologic changes in cases in which the diagnosis was exophthalmic goiter. However, they made one important observation: Of all the cases in which the clinical diagnosis was exophthalmic goiter, in those in which active hyperplasia was evident there was a higher mortality, namely, 25 per cent. It was this difference in the mortality rate which made all members of surgical clinics, at a time when the

field of thyroid surgery was being developed, loath to exclude from their statistics on surgical mortality the other groups of cases with a lower mortality rate in which the condition resembled but was distinguishable by accurate study from true exophthalmic goiter. This led to the more general use of the term hyperthyroidism which, although inclusive, readily admits subdivision into primary (exophthalmic goiter) and secondary (adenomatous goiter with hyperthyroidism) conditions. This distinction, when desirable, can be omitted in reports on mortality. (The present-day reversal in the mortality rate has obviated this objection whenever iodine is administered properly.)

Plummer,²⁸⁰ as is well known, has consistently maintained that the two clinical syndromes of exophthalmic goiter, that associated with diffuse parenchymatous hypertrophy and hyperplasia of the thyroid gland and that of adenomatous goiter in which diffuse extra-adenomatous hyperplasia is absent, are distinct clinicopathologic entities. The best presentation of the pathologic anatomy of the thyroid gland in relation to variations in its activity is contained in Plummer's article on "Functions of the Normal and Abnormal Thyroid Gland" in "Oxford Medicine" (1922). The most extensive presentation of the reasons leading up to the use of iodine in the treatment of exophthalmic goiter, the method of its administration and the results from its use are given in the Beaumont Lecture delivered by Plummer²⁸² in the autumn of 1925.

It is impossible briefly and adequately to summarize these articles, and I can only bring out here two points which are necessary in my attempt to correlate the recent experimental work, initiated by Loeb, which has resulted in producing in animals a syndrome closely resembling the syndrome of exophthalmic goiter in man: 1. Endemic goiter appears to develop as the result of an increase in the normal stimuli of potential hypothyroidism (that is, a concentration of thyroxine in the tissues slightly below normal), which gives rise to normal stimulation of the thyroid gland to make up this deficiency which develops under conditions of an insufficient supply (concentration) of iodine. Endemic goiter can be prevented by the prophylactic administration of iodine, as was conclusively shown by Marine and others; McCarrison²¹⁶ has also emphasized that contributing factors, for example, filth, insufficient diet and so forth, should, if present, be remedied. The demonstrable pathologic changes in the thyroid gland under these conditions are, first, possibly transient hypertrophy and hyperplasia followed by deposition of colloid and the formation of new acini, thus producing adenomatous goiter without hyperthyroidism. Late in life this adenomatous goiter may deliver to the tissues an excess of thyroxine normal in character which produces the hyperthyroidism of adenomatous goiter; a sudden increase in the amount of thyroxine which the adenoma-

tous or surrounding tissues delivers to the body seems at times to be initiated by the administration of iodine (Kocher's *Jod-Basedow*¹⁷²). 2. The ultimate cause of exophthalmic goiter is unknown, but evidence suggests the theory that the immediate cause is the sudden springing into activity of some unknown type of abnormal stimulation which forces the thyroid gland (which up to that time usually is normal) to make and deliver to the tissues an excessive secretion that is in part thyroxine and in part some abnormal intermediate by-product. It is the variation in the properties of these two products that makes up the variable syndrome of exophthalmic goiter before and after the administration of iodine and the abolishment of the abnormal product by iodine which is the most important factor in decreasing the mortality rate. Although Moebius in 1887 suggested that exophthalmic goiter is due to dys-thyroidism, Plummer's two-product theory is in no way related to that idea. Confusion has arisen from the fact that if this unknown stimulus to the thyroid gland suddenly develops in a subject who has had a pre-existing endemic goiter the histopathologic picture will be confusing. Of cases at the Mayo Clinic, in approximately 30 per cent in which exophthalmic goiter developed the thyroid gland had previously contained adenomatous tissue; the proportion of such cases would vary greatly in districts where endemic goiter was common from the proportion in those in which it was rare.

One of the best recent pathologic descriptions of the different forms of goiter is that of Aschoff, which was presented by him at the International Conference on Goiter in Bern in 1927. This paper should not only be read but studied. Throughout his article Aschoff repeatedly insisted on the sharp distinction between endemic goiter in its various forms and the thyroid gland in exophthalmic goiter. Unfortunately, I can give only the following brief excerpts:

Basedow's disease is no real thyroxine poisoning, that is to say, no ordinary hyperthyroidism.

Before we turn to this question and to that of the causation of goiter, we must still make brief mention of a form of struma, which really does not belong to our subject of Endemic Goiter. This is the so-called Basedow goiter, Graves' disease, or exophthalmic goiter, which makes its appearance everywhere in the world. It takes its origin independently of endemic goiter noxa. The transformations, which a Basedow thyroid gland makes manifest to us, are well enough known. It is here far less a question of a proliferation process of the thyroid tissue, as we see in the puberty swelling or even in the puberty struma, but of alterations of the follicular epithelium within the follicle. The epithelium becomes greatly enlarged, becomes almost high-cylindrical, presses forward papillary-like into the cavity of the follicle and there takes the place of the more or less disappearing colloid. In this manner the individual follicles take on the appearance of central caniculi with abnormally high epithelium. How far in the ordinary Basedow thyroid gland there is also a proper new formation of thyroid follicles

going on, must remain open in the individual case. However, this does not play so important a part. We also get here the impression that there is something wanting as regards maturity, but more in the functional than the morphological sense. The nature of the development reminds us of the parenchymatous strumas of the period of puberty, but is distinguished from it through the special prominence of the epithelial hypertrophy. Thus it happens that we can observe transition structures between the Basedow thyroid gland and the Struma parenchymatosa, although both differ greatly from each other in their outspoken forms.

In contrast to the thyroid of Graves' disease which shows marked symptoms of hyperthyroidism, in the case of the goitrous thyroid it is rather the picture of hypothyroidism with all stages down to complete cretinism. Only in a few cases does goiter exhibit hyperthyroidism. Such are usually late forms of the goiter of puberty or so-called toxic adenoma.

Marine,²²⁴ however, in a paper read at the same meeting briefly stated that "adenomata were one of many morphological states that might occur in the thyroid in Graves' disease and their presence offers no basis for assuming Graves' disease and 'toxic adenoma' are different in any essential feature."

In the general discussion following the main papers on the pathologic anatomy of the thyroid gland Helly of St. Gall stated that when he was in Vienna he found the characteristic histologic picture in cases of Basedow's disease but did not find it so often in cases so diagnosed in St. Gall. On the other hand, de Josselin de Jong of The Netherlands said that in his country there was a characteristic histologic picture in the thyroid gland of patients with Basedow's disease; the Basedow struma has no real relation to the problem of endemic goiter. Lubarsch²⁰³ of Berlin, who in 1895 was the second (Greenfield, in 1893, being the first) to outline the characteristic structure of the thyroid gland in cases of Basedow's disease, was emphatic in maintaining that the histologic picture of this disease is characteristic and of absolute diagnostic significance.

De Quervain²⁸⁶ said:

Endemic goiter is, so to say, the antagonist of the genuine Basedow. To be sure the latter occur in goitrous districts, but all the more seldom, the nearer we approach the endemic center. It accordingly is more rarely found in Bern than in Basel and affects there not more than 1 to 2 per cent of the cases of struma that are operated upon, if we consider only the native patient. . . . On the other hand, endemic struma gives us the great majority of iodine-Basedow cases. Whereas incredible quantities of iodine can be borne without any thyrotoxic disturbance by most individuals, who have normal thyroid glands, with goiter sufferers it frequently happens that daily doses of one-half to one milligram of iodine causes Jod-Basedow to develop which lasts for months if not even for years. . . . But it is also a fact that struma basedowificata produced by iodine affects only a small percentage of goiter sufferers who are taking iodine. . . .

To look upon struma basedowificata or at least the toxic adenomas as a hyperthyreosis and upon genuine Basedow as a dysthyreosis (Plummer) facilitates the explanation of many clinical observations. . . .

Friederich von Mueller ²⁶⁰ said: "The different geographical distributions of genuine Basedow's disease from the localization of endemic goiter with secondary hyperthyroidism speaks decisively for a separate position for genuine Basedow's disease. . . . We immediately meet with a difficulty—how can we decide in any individual case whether a true Basedow or a secondary hyperthyroidism is present?"

This clinical differentiation is admittedly difficult, especially in those districts where the incidence of endemic goiter is high, because under these circumstances any one in whom exophthalmic goiter develops must have a high percentage of chance of already having had one of the various forms of endemic goiter. In between a fourth and a fifth of the patients at the Mayo Clinic for whom a diagnosis of exophthalmic goiter is made there is more or less adenomatous hyperplasia, which produces a nodular goiter; the pathologic report in these cases is "adenomas in a hypertrophic parenchymatous thyroid." It is, of course, in this group that the most frequent errors in the clinical differential diagnosis occur, and in districts like Switzerland where the goiter is endemic the correct differential diagnosis in individual cases would be even more difficult. Means (1935) says that in Boston (where endemic goiter is exceedingly rare) he is not certain that there is any difference in the two diseases.

It seems obvious from a review of the literature that the pathologists have had difficulty in correlating a characteristic pathologic picture in cases of exophthalmic goiter in those clinics only where no serious attempt was made by the clinicians to make an accurate and careful differential clinical diagnosis or where one of the two diseases was disproportionately rare. It has been interesting to watch Fellows of the Mayo Foundation during their period in Plummer's goiter service attempt to make a differential diagnosis between exophthalmic goiter and adenomatous goiter with hyperthyroidism, and also to watch them separate the neuroses which simulate these syndromes. When first on the service they were usually wrong a little more than half the time; at the end of a year their preoperative diagnosis checked with the histologic reports of the section of surgical pathology in from 60 to 80 per cent of the cases. The consultant's preoperative diagnosis checked with these pathologic reports in better than 85 per cent of cases, and only the senior consultants obtained an agreement of 90 per cent or better. For twenty-five years H. S. Plummer has restudied at the end of each year all the clinical histories in which there was disagreement between the clinical diagnosis of exophthalmic goiter and the report of the pathologist as to the presence or absence of characteristic diffuse parenchymatous hypertrophy and hyperplasia. These discrepancies together with an analysis of the patient's symptoms were then discussed and studied with

his associates, and as a result there has developed a high degree of accuracy in the differential diagnosis. The opportunity of repeating such a study in this country has nearly passed because of the fact that endemic goiter is rapidly disappearing and also because the general use of iodine in the treatment of exophthalmic goiter has decreased the average intensity of the diffuse hypertrophy as well as the severity of the symptoms characteristic of the disease.

Definite advance could probably be made in the clinicopathologic correlation of thyroid disease if the surgical pathologist would institute investigation of the cytology of the thyroid gland by studying the Golgi apparatus* in the thyroid cells along the lines of the work initiated by Okkels and Marie Krogh. I shall later refer to the significance of their results but only mention here that they have demonstrated a probable, although rough, correlation between changes in the Golgi apparatus and the activity of the thyroid cells as measured by the heat production. They found the Golgi apparatus distinctly hypertrophied in exophthalmic goiter. Okkels has presented evidence to show that apparently the mitochondria, the significance of which in exophthalmic goiter has been extensively studied by Goetsch, are responsible for the original formation of the secretions, whereas the Golgi apparatus is apparently involved in the ultimate discharge.

It was Plummer's insistence on the separation of hyperthyroidism into the two syndromes which was the crucial factor in enabling him to demonstrate the fact that iodine will practically eliminate the combined medical and surgical mortality in cases of exophthalmic goiter, as shown in the previous section of this report.

Plummer was by no means the first to use or describe the beneficial effect of iodine in the treatment of exophthalmic goiter. The classic accident related by Trousseau in 1867, when by mistake he wrote a prescription for tincture of iodine instead of for tincture of digitalis, is probably the first accurate description of the effect of iodine in this disease. Cheadle (1869 and 1875), Kocher¹⁶³ (1874), Marine²²³ (1907), and, in later work which will be referred to subsequently, Waller (1914), Neisser (1920), Loewy and Zondek (1921) and probably others presented or referred to more or less extensive trials of iodine, but they were always prevented from proving the point by the fear of *Jod-Basedow* and the erroneous implication and hypothesis the name implied. Of course these futile attempts were known to Plummer²⁸¹ as well as to all acquainted with the literature.

* The Golgi apparatus consists of peculiarly staining droplets suspended in the cytoplasm of the cells, probably indicative of chemical reactions taking place at those points. In secretory types of cells, changes in size and position of these bodies can be correlated with the secretory function, and therefore they have a broad biologic significance for the histologist.

In March 1922 Plummer²⁸¹ decided that iodine should have an extensive trial under his supervision at the Mayo Clinic. The beneficial results were immediately apparent, and the first preliminary report was made by him²⁸¹ in May 1923 at the meeting of the Association of American Physicians. The first extensive report was by Plummer and me at the meeting of the Tri-State Medical Association in October 1923. Our report was based on observations on 400 cases, and it showed a definite decrease in the basal metabolic rate accompanied by a marked improvement in the general condition of the patient. Subsequent reports from the clinic confirmed the beneficial effect of iodine in the treatment of exophthalmic goiter, and it was established that 10 minims of compound solution of iodine (*liquor iodii compositus*) three times a day (a total of 2 cc. daily, containing approximately 25 mg. of iodine) was the best average dose which would abolish the characteristic intense nervous phenomena of the disease; usually lower somewhat the basal metabolic rate; decrease the pulse rate and the abnormally forceful heart action, thus slowing the abnormally increased circulation rate; abolish the capillary pulse; avert or bring the patient out of a gastro-intestinal or cerebral crisis and, finally, decrease the medical and surgical mortality rate. Although for a time iodine was used intermittently, it was soon found that such a procedure was bad, and that subsequently the patient apparently did not always respond as completely as at first. With the aforementioned dose it was found that major improvement began on the sixth or seventh day and reached the maximum on about the fourteenth day, at which time it was usually safe to operate (iodine therapy being continued without interruption); emaciated patients, however, with marked secondary organic degeneration of the liver or other organs became better surgical risks if allowed several weeks of recuperation, with a gain in weight. If for special purposes the administration of iodine was discontinued, no change was usually noted in the patient's condition for from four to six days, and then he gradually, although sometimes rapidly, became worse: The nervous phenomena returned; the basal metabolic rate rose, and the heart and circulation rates increased. This delay in reaction of from one to ten days was at first confusing, and it has served to confuse other observers and has caused misinterpretation of the effect of iodine, especially if administered alternately every ten days or two weeks. Considerable evidence accumulated that the intermittent administration of iodine is, to say the least, a technically bad and possibly even harmful procedure. No evidence was obtained to indicate that the disease was cured in the sense that the underlying cause was abolished. In fact, all evidence pointed to the fact that only the severity of the symptoms was decreased and death in the crisis prevented. In some of the cases, especially in those

in the milder or earlier stage, this decrease in severity of symptoms was equivalent to their complete abolishment; the symptoms, however, returned on cessation of iodine therapy unless the administration was maintained so long that it could be assumed that the unknown cause of the disease had spontaneously ceased to exist, as was known to occur occasionally.

To date more than 9,000 patients with true exophthalmic goiter have received as a routine at the Mayo Clinic, with relatively few exceptions for purposes of study, 10 drops of a compound solution of iodine three times a day (25 mg. of iodine) as a preoperative and postoperative procedure. Plummer reported that neither he nor his associates have seen a single case in which the reaction of the patient could be interpreted as indicating that this was too large a dose as far as the syndrome of exophthalmic goiter was concerned, although extraneous effects, like a cutaneous rash, occasionally developed. Means²⁵³ (1935) also was emphatic in his statement that he had never seen the slightest harm from the use of iodine in the treatment of exophthalmic goiter and discussed at length so-called iodine-resistant cases. In the first few years that iodine was used Plummer found that the accidental omission of the regular dose just before operation might eventuate in a postoperative crisis. One or two deaths occurred in 1922 which could be directly attributed to this omission, and in consequence the routine technic was tightened up to prevent such an occurrence. At Rochester the concern has been not with the minimal amount which would produce a detectable or measured effect in selected cases but the minimal amount which would give the greatest protection against postoperative crisis and death to the largest number of patients.

The first to confirm these results by accurate studies was the group at the Massachusetts General Hospital where Means and Richardson organized a "thyroid clinic" for the purpose of studying the proper treatment of exophthalmic goiter. Starr, Segall, Walcott and Means in 1924 reported their conclusions as follows: 1. Iodine by mouth will produce abrupt remission in most cases of exophthalmic goiter. 2. The remission is often as rapid and as extensive as that following subtotal thyroidectomy. 3. It is beyond question that iodine is the causal agent of this remission. 4. Iodine alone as now used has not been shown to be sufficient to suppress the disease permanently. 5. After a patient with exophthalmic goiter has been taking iodine a rapid rise of the basal metabolic rate and an increase of toxic symptoms occurs within from one to two weeks if it is discontinued. 6. In some cases of exophthalmic goiter iodine has no observable effect.

At the Massachusetts General Hospital Means and his associates continued the careful study just referred to and determined the minimal

amount of iodine which would produce in a few selected cases a decrease in the basal metabolic rate and in the associated phenomena of exophthalmic goiter. Thompson, Brailey, Thompson and Thorpe (1930) showed that in some cases as little as 1 minim of compound solution of iodine a day decreased the basal metabolic rate and that around this minimal dose there was more or less correspondence in the effect of iodine on the basal metabolic rate, depending on the amount used.

With regard to the minimal dose, Plummer has emphasized that the immunity of a patient with exophthalmic goiter from a postoperative crisis does not necessarily parallel the decrease in the basal metabolic rate, nor does the minimal dose which produces the former necessarily accomplish the latter; these are two distinct effects of iodine, and confusion has resulted from considering them synonymous. This point has recently been emphasized by Thompson, Taylor and Meyer (1934), who now recommend the routine use of 10 drops of compound solution of iodine three times a day to avoid fatal accidents.

Lerman and Means (1931) studied quantitatively the effect of iodine in various forms and found no demonstrable difference between iodine as a compound solution and as potassium iodide; they also demonstrated that the daily inhalation of from 2 to 4 Gm. of ethyl iodide (much, of course, being wasted or lost) was equivalent to the daily consumption of from 0.2 to 0.4 Gm. of potassium iodide. Means²⁵¹ (1933) in an excellent paper on the use of iodine emphasized especially its diagnostic value, as pointed out by Plummer, in the differential diagnosis of the milder cases of thyrotoxicosis from neurotic conditions. In the former a decrease in the basal metabolic rate with a general clinical improvement usually occurs, while no change is recognized in the latter. Other recent important reports on the value of iodine in the treatment of exophthalmic goiter are those by Jordi (1932); Winkenwerder and McEachern (1932); Schneider and Widmann³⁰⁹ (1933); Klose¹⁵⁷ (1933), who reported the important papers of the Second International Goiter Congress in Bern; Nell (1933); Breitner (1933); Gardiner-Hill (1933); Müller and Livadas (1933); Ewald (1933); Dennig and Schuelke (1934); Klose (1934; references 158 and 159); Tillgren and Sundgren (1934); Irsigler (1934); Schneider³⁰⁷ (1934), and Dautrebande.

At this point special attention must be given to the use of di-iodotyrosine in controlling the peculiar symptoms and crisis of exophthalmic goiter. Harington and Randall in 1929 isolated 3:5 di-iodotyrosine from the thyroid gland and demonstrated that practically all the iodine in the thyroid which is not thyroxine is di-iodotyrosine. Naturally the interest in the physiologic activity of this substance was increased. Drechsel (1895) isolated an iodine-containing amino-acid

from coral (*Gorgonia cavallina*) which he named iodogorgonic acid. This was proved in 1905 by Wheeler and Jamieson and in 1907 by Henze to be 3:5 di-iodotyrosine. No one had ever noted that di-iodotyrosine had any specific physiologic activity, yet because of its isolation from the thyroid gland and the fact, as Canzanelli, Harington and Randall (1929) pointed out, that it was probably the precursor of thyroxine in the synthesis of the latter by the body, its properties were properly reinvestigated.

Abelin (1931; references 1 and 2) presented evidence that tended to show that di-iodotyrosine decreases the heat production of rats fed thyroid substance, which led him to suggest that there is a normal physiologic inverse correlation between di-iodotyrosine and thyroxine. In 1933 he⁶ presented additional evidence to the effect by showing a favorable effect on the decrease of heat production following the administration of thyroxine to thyroidectomized animals. Gutman, Sloan, Gutman and Palmer (1933) prepared 30 patients for thyroidectomy by the administration of di-iodotyrosine and found it to be just as efficient as any other preparation of iodine but no more so; they concluded that it has no specific effect, as suggested by Abelin. Canzanelli and Rapport (1933) compared the calorogenic effect of di-iodotyrosine and found that while it was seven times as effective as tyrosine it caused only 4 per cent of the calorogenic effect produced by thyroxine in dogs. Means, Lerman and Salter found no calorogenic action of di-iodotyrosine in myxedematous patients. Thompson, Alper, Thompson and Dickie (1934) demonstrated that in 2 patients with myxedema 3.7 Gm. of di-iodotyrosine administered in nineteen intravenous doses over a period of three weeks caused no clinical or metabolic change; a similar experiment with 5.1 Gm. in fifteen days also caused no change; in 1935 Thompson and his associates³²⁶ possibly obtained a slight effect from 8.6 Gm. given intravenously in sixteen doses. Elmer⁸⁷ (1934) showed that di-iodotyrosine prevents hyperfunction of the thyroid gland of guinea-pigs following the administration of the thyrotropic hormone in the same degree as potassium iodide, and hence acts only in proportion to its iodine content; Delcourt-Bernard (1933) and Foster (1934) likewise found no difference between the action of di-iodotyrosine and that of other forms of iodine. At the symposium on thyroid diseases of the Royal Society (1933) in which Harington¹²⁸ and others took part no definite proof of the specific advantages of di-iodotyrosine was presented by Harington, although he stated that he favored its use in cases of exophthalmic goiter instead of iodine.

Until further and conclusive evidence is advanced of the supposed specific antithyroxine action of di-iodotyrosine, as well as its possible calorogenic action as found recently by Thompson, there is, to say the

least, no point in using it in preference to the more common and much cheaper preparations of iodine in the routine preoperative and post-operative treatment of exophthalmic goiter. It cannot be used as a substitute for desiccated thyroid or thyroxine in the treatment of myxedema, so far as present evidence indicates.

CALORIGENIC ACTION OF THYROXINE AND ALLIED PRODUCTS

That the fundamental and characteristic symptoms of hyperthyroidism are those of greatly increased metabolism was first recognized by Friedrich Müller in 1893.²⁵⁰ He noted that patients with exophthalmic goiter lost weight rapidly and that a negative nitrogen balance developed in patients on a diet containing sufficient calories to maintain weight and nitrogen equilibrium in patients with other diseases. Magnus-Levy in 1895 introduced into the clinic the scientific method of measuring the respiratory metabolism and thereby the heat production, which had been developed in the physiologic laboratories of Lavoisier, Zuntz, Rubner and Voit. Magnus-Levy thus confirmed Müller's discovery of an increased metabolism in persons with exophthalmic goiter, and in addition showed a decreased metabolism in hypothyroidism or myxedema; in 1904 he reported a five month study of the effect of various thyroid preparations and of iodine on the heat production of a myxedematous cretin. He noted and recorded the slow relapse which took from four to six weeks after thyroid medication was stopped before the heat production regained its original low level, but he was not at that time concerned with the character of the "decay curve" of which he recorded three examples.

Although Rubner in 1883 had enunciated the law that the heat production of man and of animals was proportional to the surface area, the surface area formula of Meeh ($KW^{2/3}$) was not sufficiently exact for accurate clinical work on human subjects. Therefore clinical calorimetry did not come into use as a routine procedure in the study of thyroid diseases until after DuBois and DuBois (1915; 1916) developed a more accurate height-weight formula, and Eugene DuBois and his associates at the Russell Sage Institute, utilizing in part calorimetric studies of their own but in large part the exact determinations of Benedict of the Carnegie Nutrition Laboratory of Boston, published their standards for age and sex in 1915. Following the establishment of the DuBois or, as he prefers to have them called, the Russell Sage, standards, Means at the Massachusetts General Hospital and I, first at the Peter Bent Brigham Hospital in Boston and shortly after at the Mayo Clinic (1917), stimulated the rapid development of clinical calorimetry.

One can pass over the large number of studies which then appeared first to prove the practical value of the basal metabolic rate in the

correct differential diagnosis of thyroid diseases among themselves and in sharply differentiating from them the conditions which merely simulated in a confusing way either the overactivity or the underactivity of the thyroid gland.

As I have stated, Friedrich Müller²⁵⁹ first showed that the metabolism in cases of exophthalmic goiter was increased by the finding of a negative nitrogen balance and loss of weight of patients on a diet sufficiently large both to maintain nitrogen equilibrium and to prevent loss of weight of patients with other diseases. From this observation it was concluded that a negative nitrogen balance is characteristic of the disease; that this is not true except in the stage of crisis was shown by Sandiford and me⁴² in a preliminary report in 1921 and in more complete reports in 1923⁴³ and 1924.³⁵ By means of carefully controlled experiments we showed that the nitrogen balance can be readily maintained if the dietary intake is sufficiently large to meet the requirements. To accomplish this it is necessary to give approximately twice the diet which would be sufficient to cover the basal heat production; the protein content should be from 1.5 to 3 Gm. per kilogram of body weight. This large intake of food in the older literature was often referred to as "bulimia" and was thought to be of a neurogenic nature. Sandiford and I have shown that such a large excess of food is necessary to maintain caloric and nitrogen equilibrium because of the presence of the following factors: (1) increase in basal heat production from 25 to 100 per cent above normal; (2) increase in restlessness and purposeless movements, although the patient is in bed, and (3) increase in the cost of performing work. Plummer and I had shown, by having patients walk on a treadmill with accurate measurement of the consumption of oxygen at rest and while walking, that patients with exophthalmic goiter and adenomatous goiter with hyperthyroidism are hardly more than half as efficient in their muscular movements as are normal persons. Since that report this interesting fact has been confirmed repeatedly.

Kendall (1915; 1916; 1917; 1919) isolated thyroxine in pure crystalline form in December 1914. He, in conjunction with Plummer, shortly proved in experiments on cretins and completely myxedematous patients that thyroxine is the active principle of the thyroid gland and that when administered in proper amounts it will restore such patients to a completely normal condition. In 1916²⁷⁸ and 1917²⁷⁹ Plummer noted that 10 mg. of thyroxine raised the heat production of a completely myxedematous patient weighing 70 Kg. to a normal level, and that the return to the original low level required a month or six weeks. Plummer concluded, therefore, that the normal amount of thyroxine in the body is somewhat less than 10 mg., or in the ratio of 1:7,000,000. and

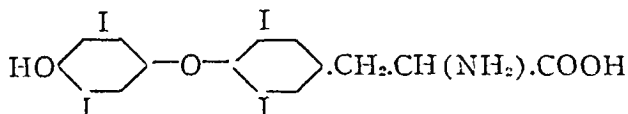
he pointed out that to produce such an immense amount of extra heat thyroxine must act in a manner similar to that of a catalyst. He also found that somewhat less than 0.5 mg. of thyroxine daily maintains the heat production at the normal level, and he therefore concluded that the amount of thyroxine made and discharged by the thyroid gland is somewhat less than this amount. As a result Plummer and, somewhat later, Means,²⁵⁰ recommended that myxedematous patients and cretins be given daily the amount of thyroxine, as desiccated thyroid standardized on the basis of its content of organic iodine, which would just maintain the normal level of heat production. They found that on the average 2 grains (0.13 Gm.) of desiccated thyroid standardized on the basis of its organic iodine content, as recommended by the United States Pharmacopeia, is the correct daily dose for the large majority of such patients.

Reid Hunt (1923), by means of his acetonitrite test, shortly discovered that desiccated thyroid produced an effect greater than the equivalent amount of thyroxine (as iodine) in protecting mice against cyanide poisoning. Some of his experiments were based on the comparison between the effect of thyroxine and desiccated thyroid when both were given orally. Thyroxine is highly insoluble, which caused part of the discrepancy; however, the discrepancy persisted in the experiments in which the effect of an oral dose of desiccated thyroid was compared to that of a subcutaneous injection of thyroxine of equivalent iodine value. This discrepancy in the calorigenic action of thyroxine and of desiccated thyroid will be considered in greater detail later.

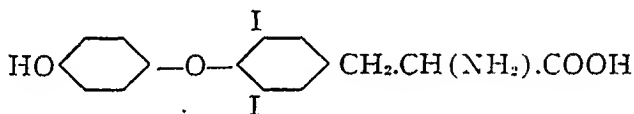
Sandiford and I with our associates (1925; 1926) carried out a balanced experiment on a completely myxedematous patient on a known diet and determined among other things the daily amount of thyroxine needed to maintain the heat production at a given level and also the peculiar characteristics of the decay curve. This part of the results was presented by Baldes and me at the Eleventh International Physiologic Congress. We were able to show that the amount of thyroxine in the body was approximately 7 mg. and that the daily amount of thyroxine needed to maintain normal heat production was 0.25 mg., both figures being slightly less than Plummer's first approximation. We demonstrated that 1 mg. of thyroxine produced by its elevation over the previous level of heat production in a completely myxedematous patient the equivalent of 1,000 large calories. We analyzed the decay curves obtained in this case and those obtained by Magnus-Levy referred to before and found that they were exponential, in our case the rate being 6 per cent per day and in Magnus-Levy's, 4 per cent per day. We showed that this exponential type of curve is consistent with the hypothesis that the extra heat production is proportional to the concentration of thyroxine in the body and consistent with the assumption that thyroxine acts as a catalyst in a monomolecular type of reaction.

Harington and Barger in 1927 synthesized 3:5:3':5'-tetra-iodo-thyronine, which has been proved to be indistinguishable by chemical or physiologic tests from thyroxine, and, in conjunction with Anderson, Harington and Lyon immediately demonstrated that the synthetic product, when given intravenously to myxedematous patients, produced exactly the same clinical as well as calorogenic effects as the natural thyroxine. Its physiologic activity has since been confirmed by many observers.

Harington¹²⁹ established the structural formula of thyroxine as follows:

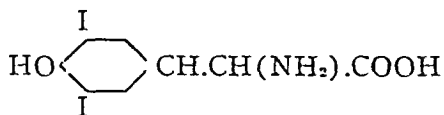


The last step in the synthesis of thyroxine is 3:5-di-iodothyronine, which has the following structural formula, with two less iodine atoms than thyroxine:



This compound, which Harington stated was easily synthesized, has been shown by Anderson, Harington and Lyon (1933) to be capable of raising the heat production of myxedematous patients in doses approximately fifty to seventy-five times as large as those of thyroxine. If further clinical experience substantiates this preliminary report and in addition demonstrates that di-iodothyronine will completely restore a myxedematous patient to a normal condition there may soon be available a very convenient preparation for therapeutic use in cases of thyroid insufficiency. Demonstration of its calorogenic effect, however, is not sufficient, because di-nitrophenol has a marked calorogenic action and yet cannot be used as a substitute for thyroxine.

The formula for 3:5 di-iodotyrosine is:

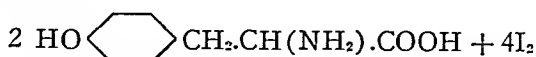


This is considered by Harington to be the probable intermediate stage in the biologic synthesis of thyroxine from tyrosine. He has shown that practically all the iodine in the thyroid gland which is not present as thyroxine is in the form of di-iodotyrosine. As I have pointed out, this substance has no (or possibly only a slight) calorogenic action on the myxedematous patient. Harington has pictured the synthesis in the body as a condensation of two tyrosine molecules in the presence of excess iodine, with the liberation of the aminopropionic acid (alanine)

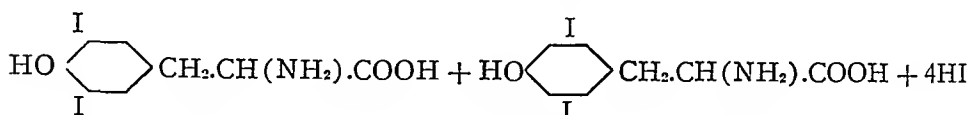
radical as a by-product either as such or as unknown degradation products. The starting point in the synthesis of thyroxine is the simple amino-acid tyrosine, which has the following structural formula:



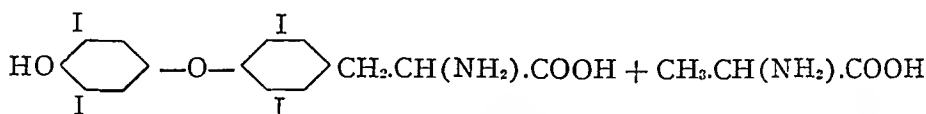
The synthesis of thyroxine then proceeds in the presence of excess iodine as follows:



two molecules of tyrosine in the presence of excess iodine form



two molecules of di-iodotyrosine which normally conjugate to form



one molecule of 3:5:3':5' tetra-iodothyronine (thyroxine) and the degradation products of the unused alanine radical.

Plummer²⁸² has suggested that the peculiar supplementary symptoms in exophthalmic goiter, which are not present in cases of adenomatous goiter with hyperthyroidism, may be due to the fact that in the synthesis of thyroxine, in the presence of an inadequate concentration of iodine and with the thyroid gland delivering an excessive amount of secretion to the body in response to an unknown stimulus, an imperfect product (or by-product) is formed and as an example suggested that an incompletely iodized thyroxine molecule may be formed at least as a part of the product. However, the administration of di-iodothyronine has not yet been demonstrated to have any such peculiar effect.

In addition to this possibility I should like to point out that in the conjugation of thyroxine in the body, as diagrammatically represented by Harington,¹²⁹ it is conceivable that the course of the series of reactions or the concentration of certain intermediate by-products with or without the benzene ring might be different under abnormal stimulation from those formed as a result of normal stimulation; for example, an amine compound might readily be formed in the presence of a low iodine concentration when the gland is working in response to the high stimulus that causes exophthalmic goiter. Under these conditions the synthetic formation of thyroxine is forced to proceed not only at an abnormally rapid rate but also frequently with a low concentration of iodine available. If such changes in conditions were made in the laboratory we should anticipate a difference in not only the quantity of the end-products but also in the quantity and possibly even in the character of

the intermediate by-products. One would not necessarily expect to find these by-products stored in the gland. In fact, an intermediate substance like tyramine, or one containing a tyramine radical, might be formed by the di-carboxylation of a tyrosine molecule and immediately be discharged into the circulation. Amines in general tend to have a toxic effect on the sympathetic nervous system. That some such or a similar abnormal by-product may be the factor in producing the exophthalmos and other characteristic symptoms, other than those due to hyperthyroidism, of the syndrome of exophthalmic goiter is rendered probable by the following experiments of Labbé and his associates and of Code and Essex.

Labbé and his associates (references 183-185) in 1931 presented before the French Academy of Science the results of an extensive series of experiments on the production of exophthalmos in animals. Their chief points may be summarized as follows: 1. Electrical stimulation of the sympathetic nerves produces protrusion of the eyeball (Bernard), but as it is accompanied by dilatation of the pupil it is not the same as in exophthalmic goiter, in which the pupil is not dilated. 2. One knows that hyperthyroidism produced by an excess of thyroxine rarely produces exophthalmos. Also, it is known that an excess of thyroxine is not necessary to produce it; however, it is possible that thyroxine plays the rôle of an adjunct and renders the conditions favorable for the production of exophthalmos by some other primary cause. 3. The sympathomimetic group of drugs differ profoundly in their action on the eyeball. Some, like epinephrine or adrenalone, produce powerful vasoconstriction but show little tendency to produce exophthalmos. Others like ephedrine, ephedrone, tyramine and para-methyl-phenyl-ethyl-amine cause marked protrusion of the eyeball. 4. Pilocarpine and hordenine cause a rapid regression of exophthalmos. 5. Thyroxine intensifies the action of some of these drugs in their power to produce exophthalmos.

Labbé and his associates also demonstrated that successive injections of thyroxine, of pilocarpine and of ephedrine will produce marked exophthalmos which persists and is accompanied by phenomena of excitation of the sympathetic and parasympathetic system.

Code and Essex from Mann's laboratory gave a demonstration of the production of exophthalmos in dogs at the recent meeting of the American Physiological Society (1935). They removed the superior orbital plate, exposing the fascia bulbi; on stimulation of the central end of the cut vagosympathetic chain a marked constriction of the fascia bulbi was clearly seen which caused marked protrusion of the eyeball. The effect was more pronounced following section of the cervical portion of the cord. Isolated strips of the fascia bulbi in Ringer's solution responded to epinephrine by definite contraction. Histologic preparations of the fascia reveal the presence of smooth muscle fibers. Further experiments along this line will be awaited with interest.

I shall now refer to a few of the more recent investigations on the thyroglobulins, especially those which have a clinical interest. A more detailed study of these and the substitution products of thyronine and the various isomers of thyroxine in which the halogen atoms are varied can be obtained in Harington's book;¹²⁹ little is yet known, however, of their detailed physiologic activity.

Hektoen, Carlson and Schulhof (1923) demonstrated thyroglobulin by the precipitation method in the lymph from the thyroid gland and later (1924) in the venous blood from the thyroid. Since 1931 Barnes, working in Carlson's laboratory, has published, with collaborators, several brief articles (references 19, 20, 21 and 23) on the physiologic activity of thyroglobulin; he found that it was absorbed undigested from closed loops of the intestine of anesthetized dogs. Barnes, Bueno and Jones also (1934) split thyroglobulin into an acid-insoluble and an acid-soluble fraction by treatment with pepsin for from twelve to twenty-four hours. These fractions contained about equal amounts of iodine, although the acid-soluble fraction contained about four times as much thyroxine (by the method of Leland and Foster); both fractions, however, had about equal activity in elevating heat production, which was approximately the same as from desiccated thyroid containing the same amount of iodine. However, the criteria used by Barnes do not necessarily indicate that the two split products would be equally effective in the treatment of myxedema.

Harington and Salter (1930) obtained as the end-product of enzymic digestion of thyroglobulin a thyroxine polypeptide which is more soluble than thyroxine and like it can be given intravenously. Lerman and Salter showed, on control myxedematous patients in Mean's clinic at the Massachusetts General Hospital, that thyroxine polypeptide produces the same calorogenic action by mouth as when given intravenously. It is therefore a convenient substance by which to compare the various thyroid compounds that cannot be injected intravenously with thyroxine, which can be given only intravenously. Lerman and Salter also showed that di-iodotyrosine peptone obtained by peptic digestion of thyroglobulin is probably inactive. They concluded that no calorogenic activity is lost in the isolation of thyroglobulin from whole thyroid gland but that di-iodotyrosine loses its activity in the first stage of digestion of thyroglobulin.

Gutman, Benedict and Palmer (1931 and 1932) analyzed by the method of Leland and Foster the thyroxine content of various thyroid preparations on the market and found a variation between the highest and lowest of 259 per cent. Means, Lerman and Salter²⁵² (1933) assayed the effect of various commercial preparations of thyroid gland on myxedematous patients and found that their calorogenic action depended on the total organic iodine rather than on the thyroxine-iodine content. As Harington and Randall (references 131 to 133) showed that apparently the whole of the acid-soluble iodine in thyroid compounds is 3:5 di-iodotyrosine (which is calorigenically inactive) and only the acid-insoluble part is thyroxine, the mechanism by which di-iodotyrosine assumes calorogenic properties when linked to the amino-acids in iodothyroglobulin is still a mystery.

Thompson and his associates³²⁵ at the Presbyterian Hospital, Chicago, carried out a valuable series of comparisons of the effect of different thyroxine compounds on the heat production of myxedematous patients. Their work is summarized in table 4.

Salter, Lerman and Means²⁹⁹ (1935) showed that the calorigenic action of the optically active isomers of thyroxine (the d- and l-thyroxine) is essentially identical when assayed on myxedematous patients. They found that the daily intravenous administration of 0.75 mg. of d- or l-thyroxine produces the same effect as a similar amount of the racemic (natural or synthetic) thyroxine and also that it is equivalent to the effect produced by the oral administration of 1 mg. of thyroxine polypeptide containing the same amount of iodine (0.5 mg.).

TABLE 4.—*Effects of Various Compounds of Thyroxine on Heat Production**

Medication†	Iodine Content	Number of Parts	Number of Administrations	Average Change in Basal Metabolic Rate, Points	Average Change in Basal Metabolic Rate in Terms of Response to Intravenous Injection of Thyroxine
10 mg. of thyroxine in alkaline solution intravenously	6.5	6	8	22	100
10 mg. of thyroxine by mouth suspended in water.....	6.5	4	4	2	6
10 mg. of thyroxine into duodenum	6.5	3	3	1	3
10 mg. of thyroxine by mouth in monosodium salt in tablets...	6.5	6	6	7	22
10 mg. of thyroxine by mouth in alkaline solution	6.5	5	5	20	63
2.83 Gm. of desiccated thyroid by mouth in tablets.....	6.5	5	5	22	69

* Reported by Thompson, Thompson, Taylor and Alper.

† The doses used were 10, 30, 40 and 100 mg.

The problem of why desiccated thyroid has a greater calorigenic action and also protects better against cyanide poisoning (Hunt acetonitrile test) than does thyroxine is therefore not explained on the basis of a more active isomer of thyroxine.

Because of these unexplained discrepancies between the thyroxine analysis of preparations of desiccated thyroid (Gutman, Benedict and Palmer) and the variation in effectiveness in the calorigenic action of thyroxine itself, as compared with desiccated thyroid, the recommendation of Means, Lerman and Salter seems sound, namely, that the present method of standardization on the total content of organic iodine as now recommended by the United States Pharmacopoeia be maintained until these discrepancies are more clearly understood.

Abelin (references 3 to 5) recently announced (1933 and 1934) that a thyroxine-like substance can be isolated in impure form from artificially iodized protein. It can be given by mouth and causes an increase in heat production even in thyroidless rats. He concluded that

there is in the organism outside the thyroid a substance which produces an action similar to thyroid substance, which he has named homothyroxine. Further information about this substance will be awaited with interest.

At the meeting of the American Society for Clinical Investigation in May 1935, Salter presented as a preliminary communication his studies on the synthesis of an artificial protein containing iodine which resembled natural thyroglobulin. He furnished me the following abstract of this important work:

Means, Lerman and Salter have determined the calorogenic effect of a series of thyroxine derivatives, namely, racemic crystalline thyroxine, crystalline l-thyroxine, crystalline d-thyroxine glycyl-thyroxine (di-peptide), thyroxine polypeptide (from sheep), thyroxine peptone (from man), whole desiccated thyroid (U. S. P.), thyroglobulin from patients with exophthalmic goiter and thyroglobulin from patients with multiple colloid adenomatous goiter. In terms of total iodine all these preparations yielded essentially identical responses when administered according to a standard procedure to patients with full-blown myxedema. Because they doubted the physiologic validity or therapeutic appropriateness of assays obtained following a single massive dose, these investigators (1) used daily doses containing 0.5 mg. of total organic iodine and (2) administered each drug in a manner which insured maximal assimilation. In consequence, the patients' basal metabolic rates became normal in about two weeks.

It was found that whole thyroid produced much more calorogenic effect than would the thyroxine which it contained. In order to corroborate further the effectiveness of both (a) the acid-insoluble or thyroxine fraction and (b) the acid-soluble or di-iodotyrosine fraction when combined in thyroglobulin, purified human thyroglobulin was digested with pepsin, and the digested material was separated into (a) the thyroxine peptone and (b) the di-iodotyrosine peptone. The thyroxine peptone (a) was found to be precisely as active calorigenically as the thyroxine which it contained. The di-iodotyrosine peptone (b) was ineffective in standard doses. Nevertheless from this relatively inert human material (b) Salter was able to obtain by peptic synthesis an artificial protein which contained iodine which resembled natural thyroglobulin and which was equally effective calorigenically in standard doses. The peptic synthesis was achieved by a modification of the procedure described by Wasteneys and Borsook. Suprisingly, the new artificial protein contained an acid-insoluble fraction (after alkaline hydrolysis) which behaved chemically like thyroxine.

ENDEMIC GOITER

Although the value of iodine in the treatment of goiter had, as I have already mentioned, been known for a long time, it was Prevost in 1849 who was apparently the first to suggest that goiter is caused by a deficiency of iodine (and bromine). Following this suggestion Chatin⁵⁵ (1851-1854) carried out extensive investigations on the presence of iodine in water, soil, plants and animals; he concluded that its deficiency is the cause of goiter and recommended to the French Academy that in districts where goiter was endemic it could be prevented by the addition of iodine to the water supply. His recommendations were not accepted,

apparently in part on the ground that his own figures for iodine in the water supply did not always correspond to the intensity of the incidence of goiter.

No further important investigations were made until McCarrison²⁰⁹ in 1902 instituted his studies on goiter in India, especially in the Himalayan mountains. In the Gilgit Fan district there were eight adjacent villages; these were situated along the course of unprotected water channels where the people were primitive and dependent on their own local produce, which was of the same kind in all the villages. The incidence of endemic goiter in the first village was 11.8 per cent, and in the last village down the stream 45.6 per cent; in a ninth village, which received its water supply from a different source, the natives were relatively free from goiter. At that time the iodine content of the soil and water was not known, but it was determined later and found not to vary in the different villages. In 1906, 1907, 1908 and 1909 McCarrison (references 210 to 215) produced goiter in young men (volunteers) who were new arrivals in these villages. To produce goiter he used the sediment from the water as it issued from the last village. The men were divided into two groups: To one group was given to drink each morning before breakfast about 6 ounces (177 cc.) of this material suspended in water which was not boiled; to the other group the same amount was given, but after the mixture had been boiled. Of 31 men who drank the unboiled suspended matter 21 had no change in the thyroid gland; 10 had noticeable goiter, and 5 had a transitory swelling. Of 31 men who drank the boiled suspended matter none had any increase in size of the thyroid gland. Those in whom goiter developed (including McCarrison himself) had associated with this condition a throbbing in the neck and feelings of fulness and discomfort. McCarrison concluded that there is a *contagium vivum* which is the responsible factor in the production of goiter.

Since these classic experiments McCarrison has continued to investigate, and in later years to supervise many investigations on, the cause and prevention of goiter in India. His experimental work has been directed along lines planned to elucidate the influence on the development of goiter in animals of such factors as filthy cages, the effect of unbalanced diet lacking or having an excess of various essential elements, the influence of vitamins and so forth, together with the influence of iodine on these various factors. He has amply demonstrated that both diet and filth (bacteria) play an important rôle in favoring the development of goiter and that they are more goitrogenic if and when the intake of iodine is low but are usually less goitrogenic or entirely innocuous in the presence of an excess of iodine.

McCarrison²¹⁷ in his address before the First International Conference on Goiter in Bern (1927) presented an excellent summary of

his experimental work and a clear discussion of the evidence for and against the two chief theories promulgated to account for endemic goiter in its various forms: (1) the theory of iodine deficiency and (2) the infectious or toxic theory. He concluded that the truth lies in a judicious blend of both. As there are various types of "simple goiter" which may prevail in the same locality, and as some persons are capable of being benefited by the prophylactic use of iodine, some are not benefited and some may be harmed by it, he is opposed to the indiscriminate use of iodine as a prophylactic measure as both unscientific and dangerous.

By this, as one gathers from his more recent papers, McCarrison does not believe (and I think all would agree with him) that only iodine should be used to control the development of goiter, but that, in addition, all contributory factors such as insanitary water supplies and foul conditions as well as deficiencies in the diet—so well brought out in his more general studies in deficiency disease—should simultaneously be remedied. He would consider it unscientific simply to give large quantities of iodine to minimize the effect of such conditions without at the same time attempting to improve them.

McCarrison has devoted the major portion of his life's work to the study of endemic goiter. Marine, in this country, has done the same thing. Many of Marine's contributions to the knowledge of the cause and means of prevention of endemic goiter are classic investigations. As with McCarrison, I cannot begin to do justice to their manifold ramifications but must limit myself to those researches which laid the foundation for the practical and effective prophylactic prevention of endemic goiter on a large scale. Marine can feel that his work has been a great success and that the results of his labors will prove an ever greater boon, not only to man himself, but to man's domestic animals.

In 1907, 1908, 1909 and 1917 Marine (references 222, 234, 238 and 244) published a series of papers on the relation of iodine to the structure and diseases of the thyroid gland, the following being his most important points: 1. All thyroid hyperplasia is anatomically, chemically (iodine) and histologically the same. 2. Iodine is necessary for normal thyroid activity. 3. The iodine control of the thyroid gland varies inversely with the degree of hyperplasia. 4. Iodine is rapidly taken up by the thyroid. 5. Exophthalmic goiter is constantly accompanied during the progressive stage of the disease by thyroid hyperplasia, and the iodine content varies inversely with the degree of hyperplasia.

About 1907 an epizootic of what appeared to be carcinoma of the thyroid broke out in many of the state and national fish hatcheries. This disease was investigated by Gaylord and Marsh and by Marine and Lenhart;²⁴⁰ Gaylord was inclined to believe that the disease was carcinoma due to an infectious factor, whereas Marine and Lenhart

(1910) proved that the disease was endemic goiter, similar to that which they had studied in mammals, and showed that it could likewise be controlled by adding compound solution of iodine to the water in the fish troughs. Gaylord confirmed the beneficial effects of iodine but also demonstrated that mercury and arsenic or the institution of sanitary conditions would interrupt the progress of the disease and restore the thyroid epithelium to a condition approximating normal, and he was particularly impressed, as McCarrison had been in his study, with the fact that the goiter (or carcinoma [?] of the thyroid) was most prevalent under insanitary conditions.

In 1888 Halsted is cited in a preliminary report by Welch as having pointed out that after partial removal of the thyroid gland in dogs compensatory hypertrophy developed in the remnant of the gland not removed which resembled somewhat the diffuse hypertrophy found in cases of exophthalmic goiter but without any of the constitutional symptoms of that disease. Halsted¹¹⁷ published the report of these experiments in detail in 1896. This method of producing compensatory hypertrophy has proved a valuable experimental method in the study of the etiology of different forms of goiter, and it was used by Loeb in his series of experiments by which he finally proved that extracts of the anterior lobe of the pituitary gland would produce in animals a syndrome closely resembling exophthalmic goiter in man; this will be described in detail later. However, in 1914 Halsted¹²⁴ attempted to repeat these experiments but was unsuccessful, and he wrote about them to Marine, who was at that time in Vienna. Marine replied and asked whether iodine had been used in the laboratory. Halsted answered that it had been used as a disinfectant of the skin on some of the dogs but not on all, and he was somewhat skeptical of that being the cause, although subsequent developments indicated that the presence in and general use of iodine around the laboratory are sufficient to permit the development of compensatory hypertrophy.

As a result of these studies, and of many others that I do not have space to mention Marine and Kimball²³⁴ began in 1917 a survey of the incidence of goiter in the school children of Akron, Ohio, from the fifth to the twelfth grades, inclusive, and instituted a carefully planned prophylactic procedure. A preliminary report of the beneficial effects secured appeared in 1918,¹⁵⁶ and the fourth²³⁵ report, which was more extensive, in 1920. The results obtained are given in table 5.

The idea of Marine and Kimball²³⁶ of initiating a prophylactic program for the prevention of endemic goiter in school children was a brilliant conception, as it avoided the possible danger of giving iodine to adults who already had goiter. As a result of its successful application to the school children of Akron popular resistance and prejudice to a more general prophylactic program was overcome in Michigan and

iodized table salt was generally introduced on the market in that state. McClure recently reported favorable results in Michigan from the use of such iodized salt.

Likewise, in Switzerland, where the dangers of *Jod-Basedow* are the greatest the prophylactic use of iodine has, wherever carried out, produced most striking results, as reported in detail by Eggenberger and in a more general way by de Quervain²⁸⁷ who has carefully and conscientiously guided the Swiss program. In Germany Fischler maintained that only ungrounded timidity prevented the rapid and complete control of endemic goiter, with all its secondary ill results of cretinism, mental and physical deficiency, stillbirth and so forth. As a result of the enthusiastic but sound efforts of Fischler and of other public health officials there is an indication that a national prophylactic program

TABLE 5.—*Summary of Record of Pupils Taking and Not Taking Iodine**

Condition of Thyroid Gland	Taking		Not Taking	
	Total	Percentage	Total	Percentage
Normal				
Unchanged.....	906	99.8	910	72.4
Increased.....	2	0.2	347	27.6
Slightly enlarged				
Unchanged.....	477	41.9	698	72.8
Increased.....	3	0.3	127	13.3
Decreased.....	659	57.8	134	13.9
Moderately enlarged				
Unchanged.....	29	20.3	57	64.0
Increased.....	0	0	21	23.6
Decreased.....	114	79.7	11	12.4
Total.....	2,190		2,305	

* Reported by Marine and Kimball.²³⁵

may be initiated in Germany to the end that "the nation be not deprived of the eugenic improvement that can occur in their goiter districts." In addition to the favorable results of goiter prophylaxis just referred to there have been many others, but of these I can only mention the very convincing results obtained by the Goiter Committee of The Netherlands as abstracted by Reith. The successful result of prophylactic measures wherever tried with practically no harmful effects has convinced most of the leaders of the medical profession of the safety of carefully supervised prophylactic methods. In recent years other lines of investigation have also led to the same conclusion—largely by the destruction of the fear of the proper use of iodine.

RECENT WORK ON THE EXPERIMENTAL DEVELOPMENT OF GOITER

Experimental Production by Cyanide of Simple (Endemic Type) Goiter in Animals.—In previous sections I have referred to the earlier experimental work on endemic goiter. A consideration of the recent

work can be conveniently begun with the accidental observation by Chesney, Clawson and Webster (1928) that goiter tended to develop in rabbits in the laboratory at Johns Hopkins which were fed a diet containing a large quantity of cabbage. In the study of this phenomenon these investigators found that enlargement of the thyroid was accompanied by a lowering of the heat production and definite cellular hyperplasia and, further, that the administration of iodine raised the heat production to the normal level and prevented thyroid hyperplasia.

Marine, Baumann and Cipra (1929) confirmed these facts and demonstrated that boiling or steaming the cabbage for thirty minutes increased its goitrogenic effect, that steamed cabbage from which 60 per cent of its weight has been removed as press-juice was practically as effective, that the press-juice itself was ineffective and that winter cabbage was more effective than summer cabbage. They concluded that the goitrogenic agent is not hexuronic acid (cevitamic acid, introduced as ascorbic acid) and also that goiter is probably not due to an absolute deficiency of iodine but only to a relative deficiency. On the other hand, drying in a current of air in vacuo causes loss of the goitrogenic agent (Marine, Baumann, Webster and Cipra,²²⁹ 1930); it can be extracted with ether or other ethereal solvents but only slightly extracted by water (Baumann, Cipra and Marine, 1931).

Since all brassicae (cabbage, brussels sprouts and so forth) produce goiter and since mustard oils (isothiocyanates) are the most characteristic constituents of these plants, it was thought the goitrogenic activity might in some way be connected with these substances or their cyanide precursors. Therefore, Marine, Baumann, Spence and Cipra²²⁸ (1931) investigated all the more common cyanide compounds and found that they all had this goitrogenic power, but that acetonitrile (methyl cyanide) produced the greatest reaction and the aromatic nitriles the least reaction; cyanamide produced only a slight reaction and sodium thiocyanate none. Marine and his co-workers concluded that these substances acted by depressing oxygen consumption and thereby increased the demand for thyroid activity.

Marine, Rosen and Cipra (1933) have shown that chronic, progressive, bilateral exophthalmos could be produced in more than 150 pre-pubertal rabbits maintained on a diet of alfalfa hay and oats by the daily intramuscular injection of from 0.05 to 0.1 cc. of methyl cyanide. Fresh vegetables fed the rabbits markedly inhibited its development. Exophthalmos may appear as early as the fourteenth day and as late as the sixtieth day after the beginning of the injections of cyanide. Males are much more susceptible, and some breeds (Dutch) are more susceptible than others (Belgian). The degree of exophthalmos obtained has been highly variable in rabbits of the same age, sex and breed, but it is always proportional to the degree of thyroid hyperplasia

(goiter) present. Removal of one superior cervical ganglion permanently abolished the exophthalmos on that side in six animals, but curettage of the medulla of both adrenal glands was without effect. Thyroidectomy in thirteen prepubertal rabbits hastened the onset of exophthalmos and increased its features after it developed.

Marine and Rosen (references 231 and 243) (1934) have been impressed with the fact that chronic and progressive exophthalmos can now be readily produced in immature animals of susceptible species by the injection of pituitary extracts and of cyanides (preferably methyl cyanide) into rabbits maintained on a diet of alfalfa hay and oats. They expressed the belief that both these means of production depend on two factors: (1) the thyrotropic hormone of the anterior lobe of the pituitary gland, in the one case by passively supplying it and in the other by stimulating the pituitary gland to produce it and (2) the existence of a relative thyroid insufficiency. The maintenance of a normal thyroid by the administration of iodine or thyroxine prevents exophthalmos caused by cyanide and pituitary extract. This indicates that normally there is a delicate physiologic balance between the need for thyroxine and the thyrotropic hormone. As regards therapy, iodine and desiccated thyroid appear to be the only logical remedies at present available, but Marine and Rosen do not believe that the results are very promising either in human exophthalmic goiter or in the experimental exophthalmos of rabbits.

Marine, Baumann, Webster and Cipra²³⁰ (1933) followed up the inhibiting effect of fresh plants previously noted by them on the goitrogenic properties of cabbage. They found that lawn grass, fresh alfalfa, skunk cabbage and steamed cabbage press-juice are antigoitrogenic. Washing brassicae with water improves their goiter-producing action, probably by removal of the goiter-preventing substances. They found that the antigoitrogenic effect of plant juice varies with the amount of reducing substance present other than glutathione. Some of the antigoitrogenic extracts contain iodine, while others do not; they are easily soluble in water or in ethyl alcohol and are precipitated by lead acetate at a p_H of from 6.8 to 7 and are partially destroyed by exposure to air and by steam at 100 C. The antigoitrogenic agent might be hexuronic acid, but it could not be glutathione. Marine, Baumann and Rosen later (1934) published the results of experiments which they interpreted as indicating that this antigoitrogenic factor actually is cevitamic acid (hexuronic acid, ascorbic acid).

Baumann, Sprinson and Metzger (1933) demonstrated that in the absence of the thyroid only 3 to 5 per cent of the cyanide of administered acetonitrile is converted into thiocyanate in rabbits, whereas with the thyroid gland intact from 27 to 35 per cent of the cyanide is transformed. The catalyzing influence of the thyroid gland is specific for

acetonitrile (methyl cyanide) and does not alter the amount of benzene cyanide or potassium cyanide converted; hence it is concerned with demethylation only.

Space prevents reference to the experiments of other observers who have confirmed many of the essential facts obtained by Marine and his associates or to those who have brought out preliminary evidence of the existence of other goitrogenic agents. That there is a difference in the reaction of different species to the influence of cyanides in producing the endemic type of goiter is indicated by the fact that Loeb and Friedman (personal communication to the author) have been unable to produce goiter in guinea-pigs by the administration of acetonitrile.

Experimental Production by Extract of the Anterior Lobe of the Pituitary Gland of a Syndrome in Animals Resembling the Syndrome of Exophthalmic Goiter in Man.—Loeb¹⁹² demonstrated in 1921 that tethelin (the active principle of the anterior lobe of the pituitary gland) has no inhibitory effect on compensatory hypertrophy of the thyroid gland, while Loeb and Kaplan¹⁹⁹ in 1924 found that the feeding of tablets of the anterior lobe of the pituitary gland (Armour) prevented compensatory hypertrophy in guinea-pigs. It was well known that hypophysectomy caused an apparent reduction in the activity of the thyroid gland.

After being stimulated by the work of Uhlenhuth and Schwartzbach on salamanders, Loeb was able to announce at the meeting of the St. Louis branch of the Society for Experimental Biology and Medicine in May 1929 that he and his associates¹⁹⁵ had obtained a hormone by making an extract of the anterior lobe of the pituitary gland which would produce compensatory hypertrophy of the thyroid gland of guinea-pigs, accompanied by loss of weight, thus indicating that there was an increased elimination of the thyroid hormone. Subsequent studies from his laboratory confirmed and extended these observations. Other investigators also contributed many important facts, the first of whom was Aron,¹³ who six months after Loeb and likewise on the guinea-pig (which Loeb in previous studies on compensatory hypertrophy had found to be a most favorable species) reported similar results at the meeting of the Société de biologie in November 1929. The evidence which has accumulated in the last five years, in great part from Loeb's laboratory, indicates that the syndrome produced in animals by the injection of the hormone of the anterior lobe of the pituitary gland is similar to (and possibly identical with) the syndrome of exophthalmic goiter in man. Even if the syndromes are comparable it does not necessarily follow that the disease of exophthalmic goiter in man is necessarily due to overactivity of the anterior lobe of the pituitary gland—it might be due to the introduction into, or formation in the body of, some other

as yet unknown substance which has the power to stimulate the thyroid gland in a similar manner.

At present an instructive series of articles is appearing under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association (references 62, 91, 225 and 317) on the general subject of the physiology of the organs of internal secretions, of which eight are devoted to the different physiologic functions of the anterior lobe of the pituitary gland and its various hormones, with complete references to the literature without, however, greatly stressing the significance of the thyroid-stimulating hormone in elucidating the problem of thyroid disease as a whole. It is now appropriate to lay the specific groundwork, the broad foundations having been presented in the previous section, on which the discovery of the thyroid-stimulating substance was made.

As I have pointed out, Marine and Lenhart (references 237 and 239) first in 1909 and in their subsequent work repeatedly stated that the administration of iodine in any form would reduce or "involute" hyperplasia of the thyroid if present in animals or prevent its development as compensatory hypertrophy following extirpation of considerable portions of the thyroid gland; this work, as has been shown, led to their work on the prevention of goiter.

About 1918 Loeb at Washington University, St. Louis, began experimental work to study the effect of the many different factors influencing the production of hypertrophy of the thyroid gland and used as his test object the compensatory hypertrophy which readily develops in guinea-pigs following the removal of considerable portions of the thyroid gland. Loeb reported ¹⁹¹ in 1920 that the administration of iodine does not diminish the intensity of compensatory hypertrophy and hyperplasia but on the contrary intensifies it. A marked increase in mitotic figures and a slight increase in the size of the cells were demonstrated. Loeb showed that the active principle of the anterior lobe of the pituitary gland known as tethelin has no effect on the development of the hyperplasia but that the administration of thyroid tablets has a marked inhibitory effect. Loeb and Kaplan ¹⁹⁹ (1923 and 1924) showed that the feeding of anterior lobe of the pituitary gland (Armour) prevents a marked or even a moderate degree of hypertrophy.

Marine ²²⁵ (1926) suggested that Loeb's "failure" to obtain "protection" by potassium iodide against compensatory hyperplasia was due to removal of too large a portion of the thyroid gland and referred to the original experiment of Marine and Lenhart ²³⁹ (1909) in which protection was obtained if not more than three fourths of the gland were removed.

Loeb ¹⁹³ (1926) stated more definitely, on the basis of a large number of experiments, that there was no question that potassium iodide does

not prevent or even diminish the compensatory hypertrophy of the thyroid gland in guinea-pigs, and distinguished between two types of response: (1) the effect on the part of the thyroid to make a normal amount of thyroxine with a low supply of iodine, and (2) the effect of some unknown stimulus which forces the thyroid to make and discharge an excess amount of thyroxine.

Marine, Deutsch and Cipra²³³ (1927) replied that iodine administered in any form and in every manner will cause involution of physiologic hyperplasia of the thyroid as well as prevent its occurrence in all orders of animals in which it has been studied: fish, birds, mammals and man. They showed that in experiments on 18 normal rabbits large doses of iodine caused a drop in the basal metabolic rate in 5, a slight increase in 2 and no change in 11. The discrepancy in the action of iodine was finally cleared up by Gray and Loeb (1928), who showed it to be due to a temporal relationship, because the hypertrophic and hyperplastic changes in guinea-pigs reached a maximum in a certain time and then receded to a normal or subnormal level. Cordonnier (in Loeb's laboratory, 1928 and 1929) demonstrated that notwithstanding the stimulating effect on the gland by causing transient hypertrophy and hyperplasia, potassium iodide does not lead to an increased output of thyroxine, as it produces no noticeable alteration in the heat production.

In 1927 an illuminating paper appeared by Uhlenhuth and Schwartzbach on the morphology and physiology of the thyroid gland of the salamander, which is so important that I shall briefly summarize it. In amphibians thyroid function consists of two main phases: (1) the elaboration of the active secretory product of the thyroid gland, the colloid, in the thyroid cells—the excretion of the colloid from the cells into the lumen of the follicles and the storage of the colloid in the follicles and (2) the excretion of the colloid from the follicles into the circulating blood. The presence of these two distinct phases is the most important characteristic. After the secretion product is formed it lies in a completely closed lumen of the follicles, and in order to effect its excretion into the circulation of the blood a special releasing-mechanism is required. During the larval period the activities of the thyroid are confined entirely to those of the first phase; the second phase, or discharge, develops suddenly at the end of the larval period and is the immediate cause of the metamorphosis. The activities of the developmental phase are elementary properties of the thyroid organ and are controlled by factors similar in nature to those controlling the activities of other glands; display of the functional phase can be effected only by the action of an extrinsic releasing-mechanism. Proceeding from a neurocirculatory hypothesis, Uhlenhuth and Schwartzbach found that no experimental procedures directed toward influencing the nervous system will hasten metamorphosis or bring about discharge of the thyroid

secretion. On the other hand, desiccated substance of the anterior lobe of the pituitary gland (Armour) will hasten metamorphosis and start the thyroid gland through the whole cycle of functional changes characteristic of thyroid glands of normal metamorphosing larvae—increase in the size of the cells, which become columnar, and a massing of the secretion granules at their apex.

In mammals there is, of course, no metamorphosis and therefore no normal, sudden releasing-mechanism (except possibly some similar mechanism in hibernating animals), but the fact that the thyroid gland of any species is susceptible to being suddenly thrown into extreme activity by a chemical stimulant (in this case presumably the pituitary hormone) appears to me of profound significance.

This paper of Uhlenhuth and Schwartzbach, as Loeb¹⁹⁴ remarked, stimulated him to reinvestigate the effect of the anterior lobe of the pituitary gland on the compensatory hypertrophy of guinea-pigs, and, thinking that some other substance might be present in the preparations of the anterior lobe previously used, he made acid and alkaline extracts from dried and powdered anterior lobes of the pituitary gland and found that both extracts will produce hypertrophy of the thyroid gland accompanied by loss of weight and other signs suggesting an increased elimination of thyroid hormone. This discovery was announced by Loeb and Basset (references 195 and 196) at the May 1929 meeting of the St. Louis Branch of the Society for Experimental Biology and Medicine. Silberberg, in October 1929, from Loeb's laboratory, confirmed and amplified these observations and reported that the stimulation of the hyperplasia and hypertrophy of the acinal epithelium was very marked, with rapid absorption of the colloid, and that the histologic picture produced resembled that of exophthalmic goiter and was very different from the comparatively mild hypertrophy and hyperplasia that Loeb had demonstrated in from fifteen to twenty days following the administration of potassium iodide. When both were given together a mosaic picture was produced but no summation effect; on the contrary, there was possibly a diminished effect of the extract of the anterior lobe of the pituitary gland. It was therefore concluded that the mechanisms which produce the effects are probably different.

Aron,¹³ at the meeting of the Société de biologie on Nov. 15, 1929, announced that extracts of the anterior lobe of the pituitary gland will produce hypertrophy of the thyroid epithelium in guinea-pigs, with absorption of the colloid, whereas extracts of other organs do not do this, and suggested that the pituitary gland controls the activity of the thyroid.

Siebert and Smith (references 312 and 313) (1930), from Loeb's laboratory, showed that the daily subcutaneous injection of either acid or alkaline extracts of the anterior lobe of the pituitary gland will

cause a rise in the basal metabolic rate which may reach a maximum of + 60 per cent in the first ten days and then return to a level of about + 15 per cent, whereas the oral administration daily of 5 grain (0.3 Gm.) pills of a substance of the anterior lobe of the pituitary gland prepared by them caused a slight gradual rise to + 20 per cent with a gradual return to normal. However, the oral administration of 5 grains a day of Armour's preparation caused a gradual rise to approximately + 60 per cent in about thirty days, but there was no tendency for the basal metabolic rate to become lower. Siebert and Smith³¹⁴ later, in 1930, showed that the rise in the basal metabolic rate caused by Armour's tablets of the anterior lobe of the pituitary gland occurred in the same manner even after partial or complete thyroidectomy. On the other hand, no rise occurred after thyroidectomy when their own extract of anterior lobe of the pituitary gland was injected, and they therefore concluded that the rise caused by their extract was dependent on the hypertrophic changes produced by it in the thyroid gland.

Cordonnier, in Loeb's laboratory, in 1929 showed that the administration of potassium iodide to normal guinea-pigs did not increase the basal metabolism; neither did it exert any noticeable effect on the rise in basal metabolism caused by the oral administration of thyroid tablets. Loeb had shown in 1920 that thyroid tablets given by mouth not only prevent compensatory hypertrophy of the thyroid gland in guinea-pigs but in addition lower the activity of the thyroid gland below normal. Correspondingly, Gray and Loeb (1928) and Gray and Rabinovitch (1929) found that thyroid tablets, when administered orally, lower the number of mitoses in the normal thyroid gland of guinea-pigs.

Aron¹⁰ in January 1930 made a further report on the histologic changes in the thyroid gland produced by the injection of extract of the anterior lobe of the pituitary gland and in April¹¹ of the same year found that these changes could be prevented by the simultaneous injection of thyroxine. Later Loeb, Basset and Friedman (1930) also demonstrated that the administration of thyroid tablets diminishes the hypertrophy which is caused by extract of the anterior lobe of the pituitary gland. The fact that the thyroid can be put at rest by the administration of thyroxine is in harmony with the previous clinical observation of Plummer (1922; 1925).

Aron¹² and Aron and Klein¹⁵ (1930) became interested in using the hypertrophic response of the thyroid of the guinea-pig to known extracts of the anterior lobe of the pituitary gland as a test object for the presence of this hormone in urine, blood and other fluids. On the assumption that such a reaction is indicative of the presence of the hormone of the anterior lobe of the pituitary gland in the blood and urine. Aron reported its presence in human urine. He then became interested

in following up the clinical application of this test, which he reported in a series of papers which appeared mostly in *Comptes rendus des séances de la Société de biologie* from 1930 to 1934. Castillo and Magdalena (1932), in Houssay's laboratory, did not find the test sensitive enough for diagnostic purposes, and its value for this purpose was absolutely denied by Krogh and Okkels¹⁷⁸ (1933). This phase of the subject is, however, outside the province of this review.

Closs, Loeb and MacKay (1931 and 1932) showed that the changes in the concentration of iodine, and especially in the concentration of the organic iodine, in the thyroid gland and in the circulating blood following the administration of extract of the anterior lobe of the pituitary gland corresponded to the changes found in the thyroid gland in cases of exophthalmic goiter. Loeb and Friedman¹⁹⁸ (1932) were the first to notice that exophthalmos develops in guinea-pigs following the use of extract of the anterior lobe of the pituitary gland. Since then this fact has been confirmed repeatedly and for nearly all types of laboratory animals used.

Siebert and Thurston (1931 and 1932) demonstrated that the increase in heat production caused by extracts of substances of the anterior lobe of the pituitary gland was much diminished by the simultaneous administration of potassium iodide. Friedgood (1934) showed that this effect of iodine was frequently only temporary and varied with dosage. On the other hand, the increase in heat production following the administration of pituitary substance (Armour) was not lowered but rather somewhat increased by the administration of potassium iodide, thus definitely showing that there is a difference in the calorogenic action of these two substances. Houssay and Rietti (1932) confirmed the increased metabolism in rats, by means of Asher's anoxemia test, by showing that rats after receiving injections of extract of the anterior lobe were more sensitive to lower concentrations of oxygen than were untreated rats; they obtained the same results later in guinea-pigs.

Houssay, Biasotti and Magdalena (1932) by injection of extract of the anterior lobe produced in dogs the hypertrophy and hyperplasia in the thyroid gland with absorption of the colloid that had been found by others in guinea-pigs. They were able to obtain this reaction in both normal and hypophysectomized dogs and also found that transplanted thyroid tissue responded in the same way. This reaction was in all instances prevented by the feeding of thyroid extract.

Benedict and Hommans (1912) showed that the heat production diminished after hypophysectomy in dogs, and since C. E. Smith's work in 1927 it has been known that hypophysectomy produces atrophy of the thyroid gland and an accumulation of colloid with a decrease in the size of the acinar cells (as pointed out in recent reviews

if the thyroid gland had been removed. Collip, Anderson and Thomson (1933) were able to produce a separation of the adrenotropic from the thyrotropic hormone. Schmeckebier (1934) found that administration of the hormone of the anterior lobe in various forms increased the proliferative activity in the adrenal cortex in guinea-pigs.

Aron¹⁴ showed in 1933 that extract of the anterior lobe, when injected into the amniotic fluid, caused hypertrophy of the fetal thyroid in the same way as in the gland after birth. Elmer (1933) showed that di-iodotyrosine was as effective as potassium iodide in preventing hypertrophy of the thyroid gland of guinea-pigs by extract of the anterior lobe of the pituitary gland. Artunde and Solari and Bueno and Barnes confirmed the previous observation of the increase in heat production following the administration of extract of the anterior lobe.

Anderson and Collip (1934) added the interesting observation that the sensitivity of rats to extract of the anterior lobe was increased by the injection of a staphylococcic vaccine. They investigated in more detail the development of resistance to extract of the anterior lobe which had been shown by Loeb and Friedman (1931 and 1932) to occur from its prolonged administration. They found that the heat production of hypophysectomized rats was reduced to approximately 26 per cent below the average normal. Following the continued administration of extract of the anterior lobe a similar decrease in metabolism, from the preliminary increase of 30 or 40 per cent to the low level of the hypophysectomized rat, stimulated them to investigate the cause of this peculiar loss of effectiveness in the extract of the anterior lobe. As a result they discovered that it was possible to obtain what they called an "antithyrotropic" substance from the serum of horses which had been treated for a long time with extract of the anterior lobe of the pituitary gland. This antithyrotropic substance of Collip and his associates does not seem to be related to the substance described by Blum under the term katechin, which has been reported to have a beneficial effect in the treatment of exophthalmic goiter; the reports concerning the value of katechin are still very meager and unconvincing.

Black (1934), working with catfish, found that the heat production was increased by the injection of extract of the anterior lobe if the fish were confined in a small aquarium without running water, but if there was a rapid exchange of water an increase in heat production did not develop. He also found that if fish not receiving injections were confined in a small aquarium with fish that had received injections hypertrophy of the thyroid would likewise develop in the former.

Friedgood in 1934 made a detailed study of the development of exophthalmos and hypertrophy of the thyroid together with the preliminary increase in heat production and the subsequent remission in the heat production following the continued use of extract of the

anterior lobe. In fact, he showed that in the late stages the heat production not only returned to normal but frequently decreased to below the original level. He found no consistent correlation between the histologic picture of the thyroid gland and the curve of heat production. His experiments were particularly clearcut from the point of view of demonstrating that the syndrome produced in guinea-pigs by extract of the anterior lobe is similar to (but not necessarily identical with) the syndrome in man known as exophthalmic goiter.

Thompson, Taylor, Thompson and Dickie in 1935 reported that the subcutaneous injection of extract of the anterior lobe into human subjects produced an increase in the basal metabolic rate in 24 of 39 patients. This increase, however, was only temporary in spite of the continued administration of the extract and in this respect resembled the results in animals. They found no increase from extract of the anterior lobe when it was given to patients with typical complete myxedema (thyroidless human subjects). In a patient with exophthalmic goiter the symptoms were markedly aggravated by the use of extract of the anterior lobe.

In addition to the various reports just noted there is a series of ten or more papers by Okkels and Marie Krogh and collaborators (1932 to 1934) in which excellent correlation is reported between alterations in the Golgi apparatus and the intensity of the symptoms in patients with exophthalmic goiter and those following the administration of extract of the anterior lobe to guinea-pigs. However, they found that these changes in the Golgi apparatus persisted after the remission which was known to develop following the prolonged use of iodine and pituitary extract, and they showed that the preoperative treatment of exophthalmic goiter with iodine (Plummer) does not influence the marked hypertrophy of the Golgi apparatus; they therefore concluded that the cellular hyperactivity probably continues unabated and assumed that the factor inducing this hypersecretion must be some extrathyroid principle and if so it must be a stimulant of nervous or humoral character.

SUMMARY

The evidence presented in this review indicates definitely that there are two different types of stimuli which, in the presence of the small amounts of iodine usually present in the laboratory diet, affect the thyroid gland in very different ways, producing in one instance a condition resembling endemic goiter in man and in the other a syndrome resembling the disease in man known as exophthalmic goiter.

The most important facts are: (1) that there is a substance (cyanide) which when administered to a susceptible animal favors the development of a diffuse colloid type of goiter and occasionally under

special conditions may cause slight exophthalmos in a limited group of susceptible animals but which produces no symptoms of hyperthyroidism, thus resembling (with the exception of the occasional slight exophthalmos just referred to) the early and milder forms of endemic goiter in man and like it can be prevented by an excess of iodine, and (2) that there is a substance (extract of the anterior lobe of the pituitary gland) which when administered to several species of laboratory animals produces a thyroid-stimulating effect characterized for a limited length of time by the development of parenchymatous hypertrophy and hyperplasia of the thyroid gland, an increase in heat production, tachycardia, increased reflex irritability and the frequent development of marked exophthalmos, all the reactions so produced closely resembling the syndrome of exophthalmic goiter in man. The administration of an excess of iodine interferes with or prevents the development of the latter as well as the former type of thyroid reaction.

Whether or not cyanide or the extract of the anterior lobe of the pituitary gland is the actual cause of endemic goiter or of exophthalmic goiter, respectively, in man is of minor significance in contrast to the great importance of the fact that there are two types of causes each of which produces very different results, thus indicating the existence of two mechanisms by which the thyroid gland can be affected. The evidence is against the assumption that cyanide is the actual goitrogenic factor which produces endemic goiter in man. Likewise, as yet there is no sound evidence that the thyroid-stimulating factor which produces exophthalmic goiter in man comes from his own pituitary gland.

Iodine deficiency, by which is meant an inadequate supply of iodine for the individual's requirements, causes endemic goiter in man. While the intake of iodine may be sufficient for one person it may not be for others under different or even under apparently similar conditions; various factors influence the individual requirements for iodine, among which are the bacterial flora of the gastro-intestinal tract resulting from filth, from overcrowding of living quarters or similar circumstances, together with a diet containing either inadequate quantities of certain essentials or possibly an excess of other elements. On the other hand, an excess of iodine prevents the development of endemic goiter with its resulting sequelae of cretinism and associated phenomena.

Certain forms of endemic goiter which have developed slowly throughout life in response to a relatively slight or potential hyperthyroidism as a result of iodine deficiency may later in life produce an excess of thyroxine, producing hyperthyroidism; this excess production of thyroxine above, and uncontrolled by, the needs of the individual requirements may in some goitrous persons apparently be precipitated by the administration of an excess of iodine.

The syndrome of exophthalmic goiter is produced by some unknown stimulus acting on the thyroid gland, possibly resembling, but not necessarily identical with, an extract which can be obtained from the anterior lobe of the pituitary gland of cattle. This syndrome is aggravated by a relative deficiency of iodine and is ameliorated by an excess of iodine. Partial thyroidectomy together with the proper administration of iodine cures the disease in a large proportion of patients with minimum mortality.

Exophthalmos and probably some of the other characteristic symptoms of exophthalmic goiter may be secondary to a peculiar irritation or stimulation of the vagosympathetic system. The fact that exophthalmos can be produced in thyroidless animals of certain species but not in others suggests that under the conditions of the experiment a sympathicostimulating substance which will produce exophthalmos can arise from sources other than the thyroid. In man, however, the sympathicostimulating substance probably arises as the result of the as yet unknown cause of the disease acting on the thyroid gland causing it to produce and discharge into the circulation (1) an excess of thyroxine and (2) under conditions of iodine deficiency some intermediate by-product having a peculiar stimulating effect on the vagosympathetic system, possibly tyramine or some similar substance. That the origin of this sympathicostimulating substance is in the thyroid is indicated in man by the fact that partial thyroidectomy, even without the administration of iodine, either abolishes or decreases in the large majority of instances the intensity of the characteristic symptoms of exophthalmic goiter attributable to this substance.

BIBLIOGRAPHY

1. Abelin, I.: Einfluss des Dijodtyrosins auf den hyperthyreotischen Stoffwechsel, *Biochem. Ztschr.* **233**:483, 1931.
2. Abelin, I.: Probleme der Schilddrüsenphysiologie, *Klin. Wchnschr.* **10**:2201 (Nov. 28) 1931.
3. Abelin, I.: Entstehung schilddrüsenähnlich wirkender Stoffe aus künstlich jodiertem Eiweiss, *Naturwissenschaften* **21**:223, 1933; *Endokrinologie* **14**:416, 1934.
4. Abelin, I.: Ueber die extrathyreoidale Entstehung thyroxinartig wirkender Jodverbindungen, *Klin. Wchnschr.* **13**:940 (June 30) 1934.
5. Abelin, I., and Florin, A.: Nichtschilddrüsenstoffe mit Schilddrüsenwirkung, *Arch. f. exper. Path. u. Pharmakol.* **171**:443, 1933.
6. Abelin, I., and Schönenberger, A.: Analyse der Dijodtyrosin und Diätwirkung bei der experimentellen Hyperthyreose, *Ztschr. f. d. ges. exper. Med.* **90**:489, 1933.
7. Anderson, E. M., and Collip, J. B.: Thyreotropic Hormone of Anterior Pituitary, *Proc. Soc. Exper. Biol. & Med.* **30**:680 (Feb.) 1933.
8. Anderson, E. M., and Collip, J. B.: Studies on the Physiology of Thyreotropic Hormone of Anterior Pituitary, *J. Physiol.* **82**:11 (Aug. 24) 1934.

9. Anderson, A. B.; Harington, C. R., and Lyon, D. M.: The Use of 3:5-Diiodothyronine in the Treatment of Myxoedema, *Lancet* **2**:1081 (Nov. 11) 1933.
10. Aron, Max: Particularités histologiques de la réaction de la thyroïde aux extraits de lobe antérieur d'hypophyse, *Compt. rend. Soc. de biol.* **103**:145 (Jan. 10) 1930.
11. Aron, Max: Action combinée de la thyroxine et de l'extrait préhypophysaire sur la thyroïde chez le cobaye, *Compt. rend. Soc. de biol.* **104**:96 (April 11) 1930.
12. Aron, Max: Méthode biologique de diagnostic des états d'hyperactivité et d'hypoactivité de la préhypophyse chez l'homme, *Compt. rend. Soc. de biol.* **105**:585 (Nov. 14) 1930.
13. Aron, Max: Action de la préhypophyse sur la thyroïde chez le cobaye, *Compt. rend. Soc. de biol.* **102**:682 (Nov. 15) 1929.
14. Aron, Max: Expériences d'injections d'extrait préhypophysaire au fœtus de cobaye in utero: Action sur la thyroïde, *Compt. rend. Soc. de biol.* **113**:446 (May 13) 1933.
15. Aron, Max, and Klein, Marc: Sur la présence dans l'urine humaine, d'une substance douée de la même action sur la thyroïde que d'extrait préhypophysaire et sur l'interprétation de la réaction de diagnostic de la grossesse, *Compt. rend. Soc. de biol.* **103**:702 (Feb. 14) 1930.
16. Artundo, Argentina, and Solari, L. A.: Action de l'extrait anté-hypophysaire sur le métabolisme basal, *Compt. rend. Soc. de biol.* **114**:385 (June 1) 1933.
17. Aschoff, Ludwig: On the Anatomy of Goiter, in Report of the International Conference on Goiter, 1927, Bern, Hans Huber, 1929, p. 1.
18. Aub, J. C., and DuBois, E. F.: Clinical Calorimetry: XIX. The Basal Metabolism of Old Men, *Arch. Int. Med.* **19**:823 (May) 1917.
19. Barnes, B. O.: The Physiological Activity of Iodine in Thyroglobulin, *Am. J. Physiol.* **101**:583 (Sept. 1) 1932.
20. Barnes, B. O.: The Excretion of Iodine in Experimental Hyperthyroidism, *Am. J. Physiol.* **103**:699 (March) 1933.
21. Barnes, B. O., and Bueno, J. G.: Studies on Thyroglobulin: II. Absorption of Thyroglobulin and Related Substances from the Alimentary Canal, *Am. J. Physiol.* **103**:570 (March) 1933.
22. Barnes, B. O.; Bueno, J. G., and Jones, Mildred: The Physiological Activity of the Thyroid Gland, *Am. J. Physiol.* **109**:5 (July 1) 1934.
23. Barnes, B. O., and Chang, T. H.: Further Studies on the Excretion of Iodine in Experimental Hyperthyroidism, *Am. J. Physiol.* **105**:3, 1933.
24. von Basedow, C. A.: Exophthalmus durch Hypertrophie des Zellgewebes in der Augenhöhle, *Wchnschr. f. d. ges. Heilk.* **6**:197 and 220, 1840.
25. Baumann, E.: Ueber das normale Vorkommen von Jod im Thierkörper, *Ztschr. f. physiol. Chem.* **21**:319, 1895-1896.
26. Baumann, E.: Ueber die Wirksamkeit des Thyroiodins, *München. med. Wchnschr.* **43**:476 (May 19) 1896.
27. Baumann, E. J.; Cipra, Anna, and Marine, David: Nature of the Goiter Producing Substance in Cabbage, *Proc. Soc. Exper. Biol. & Med.* **28**:1017 (June) 1931.
28. Baumann, E. J.; Sprinson, D. B., and Metzger, Nannette: The Relation of Thyroid to the Conversion of Cyanides to Thiocyanate, *J. Biol. Chem.* **102**:773 (Oct.) 1933.

29. Bettencourt, R., and Serrano, J. A.: Un cas de myxoedème traité par la greffe hypodermique du corps thyroïde d'un mouton, *Progrès méd.* **12**: 170, 1890.
30. Billroth, T.: *Geschwülste der Schilddrüse*, Chirurgische Klinik, 1860-1867, Berlin, 1869, p. 179.
31. Black, P. T.: Metabolic Rates of Cat-Fish Treated with Thyreotropic Hormone; abstr., *Am. J. Physiol.* **109**:10 (July) 1934.
32. Blum, F.: Ueber die antithyreoidalen Eigenschaften des Blutes und das zugrundeliegende Katechin, *Schweiz. med. Wchnschr.* **63**:777 (Aug. 12) 1933.
33. Boothby, W. M.: *Diseases of the Parathyroid and Thyroid Glands*, Oxford Medicine, New York, Oxford University Press, 1921, vol. 3, p. 831.
34. Boothby, W. M.: Parathyroid Glands: A Review of the Literature, *Endocrinology* **5**:403 (July) 1921.
35. Boothby, W. M.: The Total and Basal Metabolism in Exophthalmic Goiter, *Minnesota Med.* **7**:91 (Feb.) 1924.
36. Boothby, W. M.: Report of Two Cases in Which Treatment Has Been Given for Postoperative Parathyroid Insufficiency, *Proc. Staff Meet., Mayo Clin.* **6**:535 (Sept. 9) 1931.
37. Boothby, W. M.: Das thyreoideaproblem, *Endokrinologie* **3**:1, 1929; The Danger of Overdosage with Parathormone, *J. Clin. Investigation* **10**:176 (April 20) 1931.
38. Boothby, W. M.: A Case of Parathyroid Insufficiency, *Proc. Staff Meet., Mayo Clin.* **7**:361 (June 22) 1932.
39. Boothby, W. M., and Baldes, E. J.: Activation and Decay Curves of Thyroxin, *Proc. Staff Meet., Mayo Clin.* **1**:166 (Oct. 27) 1926.
40. Boothby, W. M.; Haines, S. F., and Pemberton, J. deJ.: Postoperative Parathyroid Insufficiency, abstr., *Proc. Staff Meet., Mayo Clin.* **5**:180 (June 25) 1930.
41. Boothby, W. M.; Haines, S. F., and Pemberton, J. deJ.: Postoperative Parathyroid Insufficiency, *Am. J. M. Sc.* **181**:81 (Jan.) 1931.
42. Boothby, W. M., and Sandiford, Irene: I. A Preliminary Note on the Food Requirement in Hyperthyroidism; II. A Comparison of Hyperthyroidism in Men and in Women, *M. Clin. North America* **5**:425 (Sept.-Nov.) 1921.
43. Boothby, W. M., and Sandiford, Irene: The Total and Nitrogenous Metabolism in Exophthalmic Goiter, *J. A. M. A.* **81**:795 (Sept. 8) 1923.
44. Boothby, W. M.; Sandiford, Irene; Sandiford, Kathleen, and Baldes, E. J.: Metabolism Studies Showing the Effect of Desiccated Thyroid and Thyroxin on a Patient with Myxedema, *Skandinav. Arch. f. Physiol.* **49**:99, 1926.
45. Boothby, W. M.; Sandiford, Irene; Sandiford, Kathleen, and Slosse, Jean: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects: I. A Method of Studying the Reserve or Deposit Protein with a Preliminary Report of the Results Obtained, *Tr. A. Am. Physicians* **40**:195, 1925; *Ergebn. d. Physiol.* **24**: 728, 1925.
46. Boothby, W. M., and Woltman, H. W.: Treatment of Postoperative Parathyroid Insufficiency: Report of a Case, *Proc. Staff Meet., Mayo Clin.* **10**:87 (Feb. 6) 1935.
47. Bubnow, N. A.: Beitrag zu der Untersuchung der chemischen Bestandtheile der Schilddrüse der Menschen und des Rindes, *Ztschr. f. physiol. Chem.* **8**:1, 1883-1884.

48. Bürkle-de la Camp, H.: Die Struma, ihre klinischen Erscheinungen und ihr histologisches Bild, *Deutsche Ztschr. f. Chir.* **230**:80, 1931.
49. Breitner, B.: Vorbemerkungen zur II. Internationalen Kropfkongferenz in Bern, August 1933, *Beitr. z. klin. Chir.* **157**:633, 1933.
50. Bueno, J. G., and Barnes, B. O.: The Effect of Loeb's Anterior Pituitary Extract upon the Basal Metabolism of Dogs, *abstr., Am. J. Physiol.* **105**:15 (July) 1933.
51. Byars, L. T.; Friedman, Hilda; Siebert, W. J., and Loeb, Leo: Are Seasonal Variations of Thyroid Gland Dependent upon Corresponding Variations in Anterior Pituitary? *Proc. Soc. Exper. Biol. & Med.* **29**:797 (April) 1932.
52. Canzanelli, Attilio, and Rapport, D.: The Comparative Effects upon Metabolism of Intravenously Injected Tyrosine, Diiodotyrosine, Diiodothyronine and Thyroxine, *Am. J. Physiol.* **103**:279 (Feb.) 1933.
53. Canzanelli, Attilio; Harington, C. R., and Randall, S. S.: The Configurative Relationship of Thyroxine and Tyrosine, *Biochem. J.* **28**:68, 1934.
54. Castillo, E. B., and Magdalena, A.: Hypophyse et thyroïde pouvoir excito-thyroïdien du sérum sanguin, *Compt. rend. Soc. de biol.* **108**:917 (Oct. 1) 1932.
55. Chatin, A.: Recherches comparatives de l'iode et de quelques autres matières dans les eaux et les égouts qui alimentent, *Compt. rend. Soc. de biol.* **35**:46; 127, 1852; Présence de l'iode dans les eaux pluviales, les eaux courantes, et les plantes des Antilles et des côtes de la Méditerranée, *Compt. rend. Soc. de biol.* **37**:723 and 958, 1853; Note sur les recherches de l'iode de l'air par la rosée, *Compt. rend. Soc. de biol.* **39**:1083, 1854.
56. Chatin, A.: Series of Investigations in Presence of Iodine in Water, Plants, Soil, Air, and So Forth, *Compt. rend. Acad. d. sc.*, pp. 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 46, 50, 60 and 82, 1850 to 1876.
57. Cheadle, W. B.: Exophthalmic Goiter (Seven Cases), *St. George's Hosp. Rep.* **4**:175, 1869; **7**:81, 1875.
58. Chesney, A. M.; Clawson, T. A., and Webster, Bruce: Endemic Goitre in Rabbits: I. Incidence and Characteristics, *Bull. Johns Hopkins Hosp.* **43**:261, 1928.
59. Closs, Karl; Loeb, Leo, and MacKay, Eaton: Effect of Acid Extract of Anterior Pituitary on Iodine Content of Blood and Thyroid in Guinea Pigs, *Proc. Soc. Exper. Biol. & Med.* **29**:170 (Nov.) 1931.
60. Code, C. F., and Essex, H. E.: The Mechanism Involved in the Production of Exophthalmos in the Dog by Vago-Sympathetic Stimulation, *Am. J. Physiol.* **112**: X (April) 1935.
61. Coindet, Charles: Découverte d'un nouveau remède contre le goitre, *Ann. de chim. et phys.* **15**:49, 1820.
62. Collip, J. B.: Glandular Physiology and Therapy: Diabetogenic, Thyrotropic, Adrenotropic and Parathyrotropic Factors of the Pituitary, *J. A. M. A.* **104**:916 (March 16) 1935.
63. Collip, J. B., and Anderson, Evelyn M.: Studies on the Thyrotropic Hormone of the Anterior Pituitary, *J. A. M. A.* **104**:965 (March 23) 1935.
64. Collip, J. B.; Anderson, Evelyn M., and Thomson, D. L.: The Adrenotropic Hormone of the Anterior Pituitary Lobe, *Lancet* **2**:347 (Aug. 12) 1933.
65. Cordonnier, J.: Effect of Potassium Iodide and Desiccated Thyroid Substance on Metabolic Rate of Guinea Pigs, *Proc. Soc. Exper. Biol. & Med.* **26**: 636 (May) 1929.

66. Crile, G. W.: Surgical Aspects of Graves' Disease with Reference to the Psychic Factor, *Ann. Surg.* **47**:864, 1908; *Tr. Am. S. A.* **26**:391, 1908. Discussion by W. J. Mayo, *ibid.*, p. 397.
67. Crile, G. W.: Graves' Disease: A New Principle of Operating Based on Study of 352 Operations, *J. A. M. A.* **56**:637 (March 4) 1911.
68. Crile, G. W.: Special Consideration of Toxic Adenoma in Relation to Exophthalmic Goiter, *Ann. Surg.* **72**:141 (Aug.) 1920.
69. Crile, G. W.: New Clinical and Experimental Studies of the Interrelations of the Thyroid, Adrenals and the Nervous System, *New England J. Med.* **198**:988 (June 28) 1928.
70. Crile, G. W.: The Adrenal Factor in Hyperthyroidism, *Surg., Gynec. & Obst.* **48**:371 (March) 1929.
71. Crile, G. W.: Clinical Analysis of 20,000 Operations on the Thyroid Gland; with Special Reference to End Results, *Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North America* **5**:392, 1930.
72. Crile, G. W.: The Mechanism by Means of Which the Thyroid and Adrenal Glands Govern Metabolism, *Tr. Am. A. Study Goiter*, 1933, p. 51.
73. Crile, G. W.: The Comparative Anatomy of the Thyroid-Adrenal-Sympathetic System, with a Discussion of the Unique Function of the Adrenal-Sympathetic System, *Tr. Am. A. Study Goiter*, 1934, p. 23.
74. Crile, G. W.: Hyperthyroidism and Associated Diseases, *Surg., Gynec. & Obst.* **58**:272 (Feb.) 1934.
75. Crile, G. W., and Lower, W. E.: The Technique of Operations on the Thyroid Gland, *Surg., Gynec. & Obst.* **34**:258 (Feb.) 1922.
76. Curling, T. B.: Two Cases of Absence of Thyroid Body, and Symmetrical Swellings of Fat Tissue at the Sides of the Neck, Connected with Defective Cerebral Development, *Tr. Med.-Chir. Soc. London* **33**:303, 1850.
77. Dautrebande, quoted by Klose.¹⁵⁷
78. Delcourt-Bernard, E.: Action comparée de la di-iodo-tyrosine et du lugol dans l'hyperthyroïde, *Compt. rend. Soc. de biol.* **114**:1397 (Nov. 25) 1933.
79. Dennig, H., and Schuelke, E.: Erfahrungen über Jodbehandlung bei Basedowscher Krankheit, *München. med. Wchnschr.* **81**:1263 (Aug. 17) 1934.
80. Drechsel, E.: Die wirksame Substance der Schilddrüse, *Centralbl. f. Physiol.* **9**:705, 1895-1896.
81. DuBois, Delafield, and DuBois, E. F.: Clinical Calorimetry: V. The Measurement of the Surface Area of Man, *Arch. Int. Med.* **15**:868 (May) 1915.
82. DuBois, Delafield, and DuBois, E. F.: Clinical Calorimetry: X. A Formula to Estimate Approximate Surface Area if Height and Weight be Known, *Arch. Int. Med.* **17**:863 (June) 1916.
83. Duval, Pierre, and Welti: A propos du traitement chirurgical de la maladie de Basedow, *Bull. et mém. Soc. nat. de chir.* **57**:288 (Feb. 18) 1931.
84. Eason, John, and Wallace, H. L.: Toxic Goiter: A Survey of Cases Treated During Ten Years, *Edinburgh M. J.* **39**:507 (Aug.) 1932.
85. Eggenberger, H.: Results of More Than Ten Year Period of Iodine Prophylaxis Against Endemic Goiter, with Comparative Study of Goiter in Switzerland and Holland, *Geneesk. bl. u. klin. en lab. v. d. prakt.* **32**:77, 1934.
86. Elmer, A. W.: L'action de la diiodotyrosine et de l'iode inorganique sur la thyroïde de cobayes soumis à des injections d'hormone préhypophysaire (thyroestimuline), *Compt. rend. Soc. de biol.* **114**:348 (June 12) 1933.
87. Elmer, A. W.: Di-Iodotyrosine and Thyroid Function, *Quart. J. Exper. Physiol.* **24**:95 (Feb.) 1934.

88. Engel, Arthur: Die Behandlung von Morbus Basedowii, *Acta med. Scandinav.* **79**:125, 1932.
89. Ewald, W.: Behandlungsergebnisse bei Morbus Basedow, *Deutsch. Ztschr. f. klin. Chir.* **239**:275, 1933.
90. von Fellenberg, T.: Untersuchungen über das Vorkommen von Jod in der Natur, *Biochem. Ztschr.* **139**:371, 1923.
91. Fishbein, Morris: *Glandular Physiology and Therapy: Introduction*, J. A. M. A. **104**:463 (Feb. 9) 1935.
92. Fischler, F.: Zur Frage der Kropfprophylaxe durch Vollsatzverwendung, *München. med. Wchnschr.* **81**:316 (March 2) 1934.
93. Fischler, F.: La importancia del yodo en el tratamiento de la glándula tiroides, en particular en la profilaxis del bocio, *Rev. méd. german.-iber.-am.* **7**:254 (July-Aug.) 1934.
94. Fischler, F.: Ueber die Notwendigkeit der Kropfverhütung durch Vollsatzanwendung in Deutschland und ihre Beziehungen zur Eugenik, *München. med. Wchnschr.* **81**:1756 (Nov.) 1934.
95. Foster, G. L.: A Comparison of the Effects of Administration of Iodide and Diiodotyrosine on the Iodine and Thyroxine Content of the Thyroid, *J. Biol. Chem.* **104**:497 (March) 1934.
96. Fox, E. L.: A Case of Myxedema Treated by Taking Extract of Thyroid by the Mouth, *Brit. M. J.* **2**:941, 1892.
97. Friedgood, H. B.: Experimental Exophthalmos and Hyperthyroidism in Guinea-Pigs, *Bull. Johns Hopkins Hosp.* **54**:48, 1934.
98. Gardiner-Hill, H.: Iodine as a Therapeutic Measure in Simple Goiter: Clinical Aspect, *Proc. Roy. Soc. Med.* **26**:874, 1933.
99. Garrison, F. H.: *History of Medicine*, ed. 3, Philadelphia, W. B. Saunders & Company, 1921, pp. 112, 141, 199 and 372.
100. Gaylord, H. R., and Marsh, M. C.: *Carcinoma of the Thyroid in the Salmonoid Fishes*, Washington, D. C., United States Government Printing Office, 1914.
101. Gley, E.: Series of Papers on Function of the Thyroid and Parathyroid Gland, *Compt. rend. Soc. de biol.* **3**:250, 366, 551, 567, 583, 841 and 843, 1891.
102. Gley, E.: Effets de la thyroïdectomie chez le lapin, *Arch. de physiol. norm. et path.* **4**:134, 1892; *Recherches sur la fonction de la glande thyroïde*, *Compt. rend. Soc. de biol.* **4**:311, 1892.
103. Gley, E.: Des troubles tardifs, consecutifs à la thyroïdectomie chez le lapin, *Compt. rend. Soc. de biol.* **4**:666, 1892.
104. Gley, E.: Nouvelle preuve de l'importance fonctionnelle des glandules thyroïdes, *Compt. rend. Soc. de biol.* **5**:396, 1893.
105. Gley, Eugene, quoted by Garrison, p. 607.
106. Gley, E., and Nicolas, A.: Premiers résultats de recherches sur les modifications histologiques des glandules thyroïdennes après la thyroïdectomie, *Compt. rend. Soc. de biol.* **47**:216 (March 23) 1895.
107. Goetsch, Emil: Functional Significance of Mitochondria in Toxic Thyroid Adenomata (Preliminary Report), *Bull. Johns Hopkins Hosp.* **27**:129 (May) 1916.
108. Grab, Werner: Die funktionelle Bedeutung der Bauelemente der Schilddrüse, *Arch. f. exper. Path. u. Pharmakol.* **172**:586, 1933.
109. Graves, R. J.: Lecture XII (on Goiter), *M. & S. J.* **7**:516, 1835.

110. Gray, S. H., and Loeb, Leo: The Effect of the Oral Administration of Potassium Iodide and Thyroid Substance on the Mitotic Proliferation and Structure of Acini in the Thyroid Gland in Guinea Pigs, *Am. J. Path.* **4**:257 (May) 1928.
111. Gray, S. H., and Rabinovitch, J.: The Effect of Combined Potassium Iodide and Thyroid Substance upon the Thyroid Gland, *Am. J. Path.* **5**:485 (Sept.) 1929.
112. Greenfield, W. S.: Some Diseases of the Thyroid Gland, *Lancet* **2**:1493 and 1553 (Dec. 16) 1893.
113. Gull, W. W.: On a Cretinoid State Supervening in Adult Life in Women, *Tr. Clin. Soc. London* **7**:180, 1873.
114. Gutman, A. B.; Benedict, E. M., and Palmer, W. W.: Assay of Thyroid by Chemical Estimation of Thyroxine Content, *Proc. Soc. Exper. Biol. & Med.* **29**:1198 (June) 1932.
115. Gutman, A. B.; Sloan, L. W.; Gutman, Ethel B., and Palmer, W. W.: The Rôle of Diiodotyrosine in Hyperthyroidism: A Comparison of the Therapeutic Effect of Diiodotyrosine with Inorganic Iodine, *J. A. M. A.* **101**:256 (July 22) 1933.
116. Halsted, W. S., quoted by Welch, W. H.: Thyroid Gland of the Dog, *M. Rec.* **34**:368 (Sept. 22) 1888.
117. Halsted, W. S.: An Experimental Study of the Thyroid Gland in Dogs, with Especial Consideration of Hypertrophy of This Gland, *Johns Hopkins Hosp. Rep.* **1**:373, 1896.
118. Halsted, W. S.: Clinical Features of Thyroid Hypertrophy, *Bull. Johns Hopkins Hosp.* **16**:288 (May 15) 1905.
119. Halsted, W. S., in discussion on Beebe, MacCallum, Barker, Preble and Kocher: Symposium on Goiter, *J. A. M. A.* **49**:1243 (Oct. 12) 1907.
120. Halsted, W. S.: Hypoparathyreosis Status Parathyreoprivus, and Transplantation of the Parathyroid Glands, *Am. J. M. Sc.* **134**:1, 1907.
121. Halsted, W. S.: Transplantation of the Parathyroid Glands, *Proc. Path. Soc. Philadelphia* **11**:109, 1908.
122. Halsted, W. S.: The Transplantation of Parathyroid Glands in Dogs, *Proc. Soc. Exper. Biol. & Med.* **5**:74, 1908.
123. Halsted, W. S.: (1) The Preliminary Ligation of the Thyroid Arteries and of the Inferior in Preference to the Superior Artery, *Tr. Am. S. A.* **31**:312 (May) 1913; (2) The Excision of Both Lobes of the Thyroid Gland for the Cure of Graves' Disease, *ibid.*, p. 319. Discussion by C. H. Mayo, *ibid.*, p. 315.
124. Halsted, W. S.: Reconsideration of the Question of Experimental Hypertrophy of the Thyroid Gland, and the Effect of Excision of This Organ upon Other Ductless Glands, *Am. J. M. Sc.* **147**:56 (Jan.) 1914.
125. Halsted, W. S.: The Operative Story of Goiter, *Johns Hopkins Hosp. Rep.* **19**:71, 1920.
126. Halsted, W. S., and Evans, H. M.: The Parathyroid Glandules: Their Blood Supply and Their Preservation in Operation upon the Thyroid Gland, *Ann. Surg.* **46**:489, 1907.
127. Harington, C. R.: Constitution and Synthesis of Desiodo-Thyroxine, *Biochem. J.* **20**:300, 1926.
128. Harington, C. R., in discussion on the use of iodine compounds in the treatment of thyroid disease, *Proc. Roy. Soc. Med.* **26**:870, 1933.
129. Harington, C. R.: *The Thyroid Gland: Its Chemistry and Physiology*, New York, Oxford University Press, 1933.

130. Harington, C. R., and Barger, G.: Chemistry of Thyroxine: Constitution and Synthesis of Thyroxine, *Biochem. J.* **21**:169, 1927.
131. Harington, C. R., and Randall, S. S.: Observations on the Iodine-Containing Compounds of the Thyroid Gland: Isolation of *dl*-3:5- Diiodotyrosine, *Biochem. J.* **23**:373, 1929.
132. Harington, C. R., and Randall, S. S.: The Chemical Assay of the Thyroid Gland, *Quart. J. Pharmacol.* **2**:501 (Oct.-Dec.) 1929.
133. Harington, C. R., and Randall, S. S.: The Isolation of *d*-3:5- Diiodotyrosine from the Thyroid Gland by the Action of Proteolytic Enzymes, *Biochem. J.* **25**:1032, 1931.
134. Harington, C. R., and Salter, W. T.: The Isolation of l-Thyroxine from the Thyroid Gland by the Action of Proteolytic Enzymes, *Biochem. J.* **24**:456, 1930.
135. Hektoen, Ludvig; Carlson, A. J., and Schulhof, Kamil: The Precipitin Reaction of Thyroglobulin: Presence of Thyroglobulin in the Thyroid Lymph of Goitrous Dogs, *J. A. M. A.* **81**:86 (July 14) 1923.
136. Helly: Explanatory Comments, in Report of the International Conference on Goiter, August 24 to 26, 1927, Bern, Hans Huber, 1929, p. 104.
137. Henze, M.: Zur Kenntnis der jodbindenden Gruppe der natürlich vorkommenden, Jodeiweiss-Körper, *Ztschr. f. physiol. Chem.* **51**:64, 1907.
138. Horsley, Victor: Note on a Possible Means of Arresting the Progress of Myxedema, Cachexia Strumipriva, and Allied Diseases, *Brit. M. J.* **1**:281, 1890.
139. Houssay, B. A.; Biasotti, A., and Magdalena, A.: Hypophyse et thyroïde: Action de l'extrait ante-hypophysaire sur l'histologie de la thyroïde du chien, *Compt. rend. Soc. de biol.* **110**:834, 1932.
140. Houssay, B. A.; Novelli, A., and Sammartino, R.: Hypophyse et thyroïde: Action excito-thyroïdienne de l'hypophyse des animaux thyroprivés, *Compt. rend. Soc. de biol.* **111**:830 (Oct. 6) 1932.
141. Houssay, B. A.; Mazzocco, P., and Biasotti, A.: Action de l'extrait antéro-hypophysaire sur l'iode thyroïdien, *Compt. rend. Soc. de biol.* **111**:82 (June 2) 1932.
142. Houssay, B. A., and Rietti, C. T.: Hypophyse et thyroïde: Estrait de lobe antérieur d'hypophyse et sensibilité à l'anoxémie, *Compt. rend. Soc. de biol.* **110**:144 (April 7) 1932.
143. Houssay, B. A., and Rietti, C. T.: Hypophyse et thyroïde: Nouvelles expériences sur l'extrait antéro-hypophysaire et résistance à l'anoxémie, *Compt. rend. Soc. de biol.* **111**:80 (June 2) 1932.
144. Hunt, Reid: The Comparative Physiological Activity of Thyroid and Thyroxin, *J. Pharmacol.* **21**:199 (April) 1923.
145. Hutchison, Robert: The Chemistry of the Thyroid Gland and the Nature of Its Active Constituent, *J. Physiol.* **20**:474, 1896.
146. Hutchison, Robert: Further Observations on the Chemistry and Action of the Thyroid Gland, *J. Physiol.* **23**:178 (July 26) 1898.
147. Irsigler, F. J.: Ueber die Wirkung der Lugoschen Lösung auf die hyper- und dysthyreotische Schilddrüse, *Deutsche Ztschr. f. Chir.* **242**:689 (May) 1934.
148. Joll, C. A.: Diseases of the Thyroid Gland with Special Reference to Thyrotoxicosis, St. Louis, C. V. Mosby Company, 1932.
149. Jordi, A.: The Biologic Value, Iodine Content, Histologic, Structural and Clinical Picture of Goiter, *Arch. Int. Med.* **49**:541 (April) 1932.

150. Joslin, E. P., and Lahey, F. H.: Diabetes and Hyperthyroidism, *Am. J. M. Sc.* **176**:1 (July) 1928.
151. de Josselin de Jong, R.: Goiter in The Netherlands in Report of International Conference on Goiter, August 24 to 26, 1927, Bern, Hans Huber, 1929, p. 108.
152. Kendall, E. C.: (a) The Isolation in Crystalline Form of the Compound Containing Iodin, Which Occurs in the Thyroid: Its Chemical Nature and Physiologic Activity, *J. A. M. A.* **64**:2042 (June 19) 1915.
153. Kendall, E. C.: The Active Constituent of the Thyroid: Its Isolation, Chemical Nature and Physiologic Action, *Collected Papers of Mayo Clinic* **8**:513, 1916.
154. Kendall, E. C.: The Thyroid Hormone, *Collected Papers of Mayo Clinic* **9**:309, 1917.
155. Kendall, E. C.: Isolation of the Iodine Compound Which Occurs in the Thyroid, *J. Biol. Chem.* **39**:125 (Aug.) 1919.
156. Kimball, O. P., and Marine, David: The Prevention of Simple Goiter in Man, *Arch. Int. Med.* **22**:41 (July) 1918.
157. Klose, H.: Bericht über die II Internationale Kropfkongferenz in Bern, *Deutsche med. Wchnschr.* **59**:1512 (Sept.) 1933.
158. Klose: Mitteilungen zur Klinik der Hyperthyreosen, *Endokrinologie* **13**:352, 1934.
159. Klose: Die II Internationale Kropfkongferenz in Bern vom 10-12 August, 1933, *Endokrinologie* **13**:366, 1934.
160. Kocher, Albert: Ueber Morbus Basedowi, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **9**:1, 1902.
161. Kocher, Albert: Ueber die Ausscheidung des Jods im menschlichen Harn und ihre Beziehung zum Jodgehalt und zur Verkleinerung der Strumen: Ein Beitrag zur Physiologie der Schilddrüse, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **14**:359, 1905.
162. Kocher, Albert: Ergebnisse histologischer und chemischer Untersuchungen von 160 Basedowfällen, *Arch. f. klin. Chir.* **92**:442, 1910.
163. Kocher, Theodor: Zur Pathologie und Therapie des Kropfes, *Deutsche Ztschr. f. Chir.* **4**:417, 1874.
164. Kocher, Theodor: Die Indicationen zur Kropfexstirpation beim gegenwärtigen Stande der Antisepsis, *Cor.-Bl. f. schweiz. Aerzte* **12**:225, 1882.
165. Kocher, Theodor: (b) Ueber Kropfexstirpation und ihre Folgen, *Arch. f. klin. Chir.* **29**:254, 1883.
166. Kocher, Theodor: Die Schilddrüsenfunction im Lichte neuerer Behandlungsmethoden verschiedener Kropfformen, *Cor.-Bl. f. schweiz. Aerzte* **15**:3 (Jan.) 1895.
167. Kocher, Theodor: Bericht über 1000 Kropfexcisionen, *Verhandl. d. deutsch. Gesellsch. f. Chir.* **24**:29 (April 17) 1895.
168. Kocher, Theodor: Bericht über einen zweites Tausend Kropfexcisionen, *Arch. f. klin. Chir.* **64**:454, 1901.
169. Kocher, T.: Die Therapie des Kropfes, *Deutsche Klin.* **8**:1115, 1904.
170. Kocher, Theodor: Ueber ein drittes Tausend Kropfexstirpationen, *Arch. f. klin. Chir.* **79**:786, 1906.
171. Kocher, T.: The Pathology of the Thyroid Gland, *Brit. M. J.* **1**:1261 (June 2) 1906.
172. Kocher, Theodor: Ueber Jodbasedow, *Arch. f. klin. Chir.* **92**:1166, 1910.
173. Kocher, Theodor: Ueber Basedow: Einleitender Vortrag zur Discussion, *Arch. f. klin. Chir.* **96**:403, 1911.

174. Kocher, Theodor: Ueber Kropf und Kropfbehandlung, *Deutsche med. Wchnschr.* **2**:1265 (July 4) and 1313 (July 11) 1912.
175. Krogh, Marie, and Lindberg, Anna L.: Studies on the Thyroid Gland: II. The Physiological Activity of Iodine in Thyroxin and, in Normal and Pathological Thyroid Glands, *Acta path. et microbiol. Scandinav.* **9**:21, 1932.
176. Krogh, Marie; Lindberg, A. L., and Okkels, Harald: Studies on the Thyroid Gland: III. Experimental Hyperactivity of the Thyroid Gland, *Acta path. et microbiol. Scandinav.* **9**:37, 1932.
177. Krogh, Marie, and Okkels, Harald: Sur l'histophysiologie du corps thyroïde: Stades initiaux de la sécrétion thyroïdienne, *Compt. rend. Soc. de biol.* **112**:1694 (April 1) 1933.
178. Krogh, M., and Okkels, H.: L'hormone thyroïdienne préhypophysaire est-elle présente dans l'urine? *Compt. rend. Soc. de biol.* **113**:635 (April 28) 1933.
179. Krogh, Marie, and Okkels, Harald: Studies on the Thyroid Gland: V. The Thyroid Stimulating Hormone from the Anterior Pituitary; Some Chemical Properties, *Acta path. et microbiol. Scandinav.* **10**:126, 1933.
180. Krogh, Marie, and Okkels, Harald: L'hormone thyroïdienne stimulante de la préhypophyse, *Compt. rend. Soc. de biol.* **116**:255 (April 12) 1934.
181. Labbé, Marcel, and Azerad: Traitement chirurgical de la maladie de Basedow, *Bull. et mém. Soc. nat. de chir.* **57**:136 (Jan. 28) 1931.
182. Labbé, Marcel: Traitement chirurgical de la maladie de Basedow, *Bull. et mém. Soc. nat. de chir.* **57**:444 (March 18) 1931.
183. Labbé, Marcel; Boulin, Raoul; Azerad, E., and Justin-Besançon, L.: Exophtalmie et goitre congénitaux sans hyperthyroïdie, *Bull. et mém. Soc. méd. d. hôp. de Paris* **1**:852 (May 27) 1932.
184. Labbé, Marcel; Villaret, Maurice; Justin-Besançon, L., and Soulié, P.: Etude sur la pathogénie des exophtalmies de type basedowien (1), *Bull. et mém. Soc. méd. d. hôp. de Paris* **2**:1897 (Sept. 11) 1931.
185. Labbé, Marcel; Villaret, Maurice; Comandon, J.; Justin-Besançon, L.; Kohler, Denise; Schiff-Wertheimer, and Soulié, P.: Sur les méthodes d'étude des exophtalmies expérimentales (avec projection cinématographique), *Compt. rend. Soc. de biol.* **108**:478 (Oct. 24) 1931; *Compt. rend. Acad. d. sc.* **192**:260, 1931.
186. Lahey, F. H.: Thyroid Diseases, *New England J. Med.* **210**:1016 (May 10) 1934.
187. Lahey, F. H., and Hurxthal, L. M.: Postoperative End-Results in Three Hundred Thyrocardiacs, *Am. J. Surg.* **24**:225, 1934.
188. Leland, Jessica P., and Foster, G. L.: A Method for the Determination of Thyroxine in the Thyroid, *J. Biol. Chem.* **95**:165 (Feb.) 1932.
189. Lerman, Jacob, and Means, J. H.: Iodine in Exophtalmic Goiter: A Comparison of the Effect of Ethyl Iodid and Potassium Iodid with That of Lugol's Solution, *Am. J. M. Sc.* **181**:744, 1931.
190. Lerman, J., and Salter, W. T.: The Calorigenic Action of Thyroid and Some of Its Active Constituents, *Tr. Am. A. Study of Goiter* 1933, p. 160; *Endocrinology* **18**:317 (May-June) 1934.
191. Loeb, Leo: Studies on Compensatory Hypertrophy of the Thyroid Gland: The Influence of Iodine on Hypertrophy of the Thyroid Gland, *J. M. Research* **41**:481, 1920.

192. Loeb, Leo: Studies on Compensatory Hypertrophy of the Thyroid Gland: The Effect of the Administration of Thyroid, Thymus Gland and Tethelin and of a Meat Diet on the Hypertrophy of the Thyroid Gland in Guinea-Pigs, *J. M. Research* **42**:77, 1921.
193. Loeb, Leo: Studies on Compensatory Hypertrophy of the Thyroid Gland: Further Investigation of the Influence of Iodin on Hypertrophy of the Thyroid Gland with an Interpretation of the Differences in the Effects of Iodin on the Thyroid Gland Under Various Pathologic Conditions, *Am. J. Path.* **2**:19, (Jan.) 1926.
194. Loeb, L.: Studies on Compensatory Hypertrophy of the Thyroid Gland: A Comparison Between the Effect of Administration of Thyroxin, Thyroid and Anterior Pituitary Substance on the Compensatory Hypertrophy of the Thyroid Gland in the Guinea-Pig, *Am. J. Path.* **5**:71 (Jan.) 1929.
195. Loeb, Leo, and Bassett, R. B.: Effect of Hormones of Anterior Pituitary on Thyroid Gland in the Guinea-Pig, *Proc. Soc. Exper. Biol. & Med.* **26**: 860 (June) 1929.
196. Loeb, Leo, and Bassett, R. B.: Comparison of Effects of Various Preparations of Anterior Pituitary Gland on Thyroid of Guinea-Pig, *Proc. Soc. Exper. Biol. & Med.* **27**:490 (March) 1930.
197. Loeb, Leo.; Bassett, R. B., and Friedman, Hilda: Further Investigations Concerning the Stimulating Effect of Anterior Pituitary Gland Preparations on the Thyroid Gland, *Proc. Soc. Exper. Biol. & Med.* **28**:209 (Dec.) 1930.
198. Loeb, Leo, and Friedman, Hilda: Exophthalmos Produced by Injections of Acid Extract of Anterior Pituitary Gland of Cattle, *Proc. Soc. Exper. Biol. & Med.* **29**:648 (Feb.) 1932.
199. Loeb, Leo, and Kaplan, E. E.: Studies on Compensatory Hypertrophy of the Thyroid Gland: The Effect of Feeding Anterior Lobe of the Pituitary Gland on the Hypertrophy of the Thyroid Gland in the Guinea-Pig, *J. M. Research* **44**:557 (Sept.) 1924.
200. Loeser, Arnold: Hypophysenvorderlappen und Schilddrüse: Die Wirkung der thyreotropen Substanz des Hypophysenvorderlappens auf die Nebennieren, *Arch. f. exper. Path. u. Pharmacol.* **173**:62, 1933.
201. Loewy, A., and Zondek, Hermann: Morbus Basedowii und Jodtherapie: Klinische und gasanalytische Beobachtungen, *Deutsche med. Wchnschr.* **47**:1387 (Nov.) 1921.
202. Lubarsch, O.: Ueber die Schilddrüsenveränderungen bei Morbus Basedowii, *Verhandl. d. Gesellsch. deutsch. Naturf. u. Aertze*, 1895.
203. Lubarsch, O., in discussion on Helly and Biedel, in Report of International Conference on Goiter, August 24 to 26, 1927, Bern, Hans Huber, 1929, p. 116.
204. MacCallum, W. G.: The Pathology of Exophthalmic Goiter, *J. A. M. A.* **49**:1158 (Oct. 5) 1907.
205. MacCarty, W. C.: Pathologic Anatomy of Goiter (a Macroscopic and Microscopic Study of Fresh Material from 2500 Cases), *New York State J. Med.* **12**:595 (Oct.) 1912.
206. MacCarty, W. C.: Goiter and Its Relation to Its Structural and Physiologic Units, *Surg., Gynec. & Obst.* **16**:406 (April) 1913.
207. MacCarty, W. C.: Pathologic Classification of Goiter and Its Clinical Significance, *Ann. Int. Med.* **5**:178 (Aug.) 1931.

208. MacKenzie, H. W. G.: A Case of Myxedema Treated with Great Benefit by Feeding with Fresh Thyroid Glands, *Brit. M. J.* **2**:940, 1892.
209. McCarrison, R.: Observations on Endemic Goiter in the Chitral and Gilgit Valleys, *Tr. Med. Chir. Soc. London* **89**:437, 1906.
210. McCarrison, Robert: Observations on Endemic Goitre in the Chitral and Gilgit Valleys, *Lancet* **1**:1110 (April 21) 1906.
211. McCarrison, R.: Observations on Endemic Cretinism in the Chitral and Gilgit Valleys, *Lancet* **2**:1275 (Oct. 31) 1908.
212. McCarrison, Robert: Observations on the Amoebae in the Intestines of Persons Suffering from Goiter in Gilgit, *Quart. J. Micr. Sc.* **53**:723 (July) 1908-1909.
213. McCarrison, Robert: Further Researches on the Etiology of Endemic Goiter, *Quart. J. Med.* **2**:279 (April) 1908-1909.
214. McCarrison, Robert: Observations on Endemic Cretinism in the Chitral and Gilgit Valleys, *Proc. Roy. Soc. Med.* **2**:1 (Oct. 27) 1909; *Indian M. Gaz.* **43**:441, 1908.
215. McCarrison, Robert: A Summary of Further Researches on the Etiology of Endemic Goiter, *Proc. Roy. Soc. Med.* **81**:31, 1909.
216. McCarrison, Robert: *The Thyroid Gland in Health and Disease*, New York, William Wood & Company, 1918.
217. McCarrison, Robert: The Aetiology and Epidemiology of Endemic Goitre, in Report of the International Conference on Goiter, August 24 to 26, 1927, Bern, Hans Huber, 1929, p. 280.
218. McClendon, J. F.: The Distribution of Iodine with Special Reference to Goiter, *Physiol. Rev.* **7**:189 (April) 1927.
219. McClure, R. D.: Thyroid Surgery as Affected by the Generalized Use of Iodized Salt in an Endemic Goitre Region: Preventive Surgery, *Ann. Surg.* **100**:924 (Nov.) 1934.
220. Maes, Urban; Boyce, F. F., and McFetridge, Elizabeth M.: Clinical Problems of Thyroid Disease in a Non-Endemic Area, *Am. J. Surg.* **24**:232, 1934.
221. Magnus-Levy, Adolf: Ueber den respiratorischen Gaswechsel unter dem Einfluss der Thyreoidea sowie unter verschiedenen pathologischen Zuständen: Kurze Mittheilung, *Berl. klin. Wchnschr.* **32**:650 (July 29) 1895.
222. Marine, David: The Histology of the Thyroid in Simple and Toxic (Exophthalmic) Goitre, with Remarks on Similar Changes in the Dog, *Cleveland M. J.* **6**:45, 1907.
223. Marine, David: On the Occurrence and Physiological Nature of Glandular Hyperplasia of the Thyroid (Dog and Sheep), Together with Remarks on Important Clinical (Human) Problems, *Bull. Johns Hopkins Hosp.* **18**:359 (Sept.) 1907.
224. Marine, D.: Certain Features of the Morphological Pathology of Endemic Goiter, in Report of the International Conference on Goiter, August 24 to 26, 1927, Bern, Hans Huber, 1929, p. 59.
225. Marine, David: Control of Compensatory Hyperplasia of the Thyroid of Guinea-Pigs by the Administration of Iodine, *Arch. Path.* **2**:829 (Dec.) 1926.
226. Marine, David; Baumann, E. J., and Cipra, Anna: Studies on Simple Goiter Produced by Cabbage and Other Vegetables, *Proc. Soc. Exper. Biol. & Med.* **26**:822, 1929.
227. Marine, David; Baumann, E. J., and Rosen, S. W.: Effect of Ascorbic Acid on Thyroid and Suprarenals of Guinea-Pigs, *Proc. Soc. Exper. Biol. & Med.* **31**:870 (April) 1934.

228. Marine, David; Baumann, E. J.; Spence, A. W., and Cipra, Anna: Further Studies on Etiology of Goiter with Particular Reference to Action of Cyanides, *Proc. Soc. Exper. Biol. & Med.* **29**:772 (March) 1932.
229. Marine, David; Baumann, E. J.; Webster, Bruce, and Cipra, Anna: Effect of Drying in Air on Goiter-Producing Substance in Cabbage, *Proc. Soc. Exper. Biol. & Med.* **27**:1025 (June) 1930.
230. Marine, David; Baumann, E. J.; Webster, Bruce, and Cipra, Anna: Occurrence of Antigoitrous Substances in Plants, *J. Exper. Med.* **57**:121 (Jan.) 1933.
231. Marine, David, and Rosen, S. H.: The Exophthalmos of Graves' Disease: Its Experimental Production and Significance, *Am. J. M. Sc.* **188**:565 (Oct.) 1934.
232. Marine, David; Rosen, S. H., and Cipra, Anna: Further Studies on the Exophthalmos in Rabbits by Administration of Cyanide, *Proc. Soc. Exper. Biol. & Med.* **30**:649, 1933.
233. Marine, David; Deutsch, Max, and Cipra, Anna: The Effect of Large Doses of Iodine Heat Production in Rabbits, *Proc. Soc. Exper. Biol. & Med.* **24**:657, 1927.
234. Marine, David, and Kimball, O. P.: The Prevention of Simple Goiter in Man: A Survey of the Incidence and Types of Thyroid Enlargements in the Schoolgirls of Akron (Ohio), from the Fifth to the Twelfth Grades, Inclusive; The Plan of Prevention Proposed, *J. Lab. & Clin. Med.* **3**:40 (Oct.) 1917.
235. Marine, David, and Kimball, O. P.: Prevention of Simple Goiter in Man, *Arch. Int. Med.* **25**:661 (June) 1920.
236. Marine, David, and Kimball, O. P.: Goiter Survey Work in Ohio; Incidence of Simple Goiter in School Children of Cleveland, Akron, and Warren, Ohio State M. J. **16**:757 (Oct.) 1920.
237. Marine, David, and Lenhart, C. H.: Colloid Glands (Goitres): Their Etiology and Physiological Significance, *Bull. Johns Hopkins Hosp.* **20**:131 (May) 1909.
238. Marine, David, and Lenhart, C. H.: Relation of Iodin to the Structure of Human Thyroids: Relation of Iodin and Histologic Structure to Diseases in General; to Exophthalmic Goiter; to Cretinism and Myxedema, *Arch. Int. Med.* **4**:440 (Nov.) 1909.
239. Marine, David, and Lenhart, C. H.: Effects of the Administration or the Withholding of Iodin-Containing Compounds in Normal, Colloid or Actively Hyperplastic (Parenchymatous) Thyroids of Dogs: Some Experiments on (Congenital) Prenatal Thyroid Hyperplasia in Dogs; Remarks on the Clinical Manifestations Associated with Marked Thyroid Hyperplasia, *Arch. Int. Med.* **4**:253 (Sept.) 1909.
240. Marine, David, and Lenhart, C. H.: On the Occurrence of Goiter (Active Thyroid Hyperplasia) in Fish, *Bull. Johns Hopkins Hosp.* **21**:95 (April) 1910.
241. Marine, David, and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter: The Anatomical and Physiological Relations of the Thyroid Gland to the Disease; the Treatment, *Arch. Int. Med.* **8**:265 (Sept.) 1911.
242. Marine, David, and Rosen, S. H.: Exophthalmos in Thyroidectomized Guinea-Pigs by Thyrotropic Substance of Anterior Pituitary, and the Mechanism Involved, *Proc. Soc. Exper. Biol. & Med.* **30**:901 (April) 1933.
243. Marine, David, and Rosen, S. H.: Effect of Thyrotropic Hormone on Auto and Homeotransplants of the Thyroid and Its Bearing on Questions of Secretory Nerves, *Am. J. Physiol.* **107**:677 (March) 1934.

244. Marine, David, and Williams, W. W.: The Relation of Iodin to the Structure of the Thyroid Gland, *Arch. Int. Med.* **1**:349 (May) 1908.
245. Mayo, C. H.: The Surgical Treatment of Goiter, *J. A. M. A.* **42**:1059 (April 23) 1904.
246. Mayo, C. H.: Thyroidectomy for Exophthalmic Goiter: Based Upon Forty Operated Cases, *Tr. Am. S. A.* **22**:210, 1904.
247. Mayo, C. H.: A Consideration of the Mortality in One Thousand Operations for Goiter, *South. Surg. & Gynec. Tr.* **21**:275 (Dec.) 1908; *Surg., Gynec. & Obst.* **8**:237 (March) 1909.
248. Mayo, C. H.: A Consideration of Surgical Methods of Treating Hyperthyroidism, *M. Rec., Collected Papers*, Dec. 31, 1910, p. 1173.
249. Mayo, C. H.: Surgery of the Thyroid; Observation on Five Thousand Operations, *J. A. M. A.* **61**:10 (July 5) 1913.
250. Means, J. H.: The Use and Abuse of Thyroid, *Boston M. & S. J.* **187**:164 (Aug. 3) 1922.
251. Means, J. H.: The Diagnostic Use of Iodine in Thyrotoxicosis, *Ann. Int. Med.* **7**:439 (Oct.) 1933.
252. Means, J. H.; Lerman, J., and Salter, W. T.: The Rôle of Thyroxine, Iodine and Total Organic Iodine in the Calorigenic Action of Whole Thyroid Gland, *J. Clin. Investigation* **12**:683 (July) 1933.
253. Means, J. H., and Lerman, Jacob: Action of Iodine in Thyroxicosis, with Special Reference to Refractoriness, *J. A. M. A.* **104**:969 (March 23) 1935.
254. Means, J. H.; Lerman, J., and Salter, W. T.: The Rôle of the Thyroxine, Iodine and Total Organic Iodine in the Calorigenic Action of Whole Thyroid Gland, *J. Clin. Investigation* **12**:683 (July) 1933.
255. Meeh, K.: Oberflächenmessungen des menschlichen Körpers, *Ztschr. f. Biol.* **15**:425, 1879.
256. Mikulicz, J.: Beitrag zur Operation des Kropfes, *Wien. med. Wchnschr.* **36**:1, 40, 70, 97, 1886.
257. Moebius, P. J.: Ueber das Wesen der Basedow'schen Krankheit, *Centralbl. f. Nervenlh.* **10**:225, 1887.
258. Morawitz, P.: Morbus Basedow, *Arch. f. klin. Chir.* **167**:359, 1931.
259. Müller, F.: Beiträge zur Kenntnis der Basedow'schen Krankheit, *Deutsches Arch. f. klin. Med.* **51**:335, 1893.
260. von Mueller, Friederich: The Pathological Physiology of the Thyroid, in Report of the International Conference on Goiter, August 24 to 26, 1927, Bern, Hans Huber, 1929, p. 204.
261. Müller, P., and Livadas, K.: Ueber die Behandlung der Basedowschen Krankheit mit Jod und Arsen, *München. med. Wchnschr.* **80**:1471 (Sept.) 1933.
262. Murray, G. R.: The Life-History of the First Case of Myxoedema Treated by Thyroid Extract: Note on Treatment of Myxedema by Hypodermic Injections of an extract of Thyroid Gland of Sheep, *Brit. M. J.* **1**:359 (March 13) 1920.
263. Neisser, E.: Ueber Jodbehandlung bei Thyreotoxikose, *Berl. klin. Wchnschr.* **57**:461 (May) 1920.
264. Nell, Walter: Die präoperative Behandlung des Morbus Basedow, *Beitr. z. klin. Chir.* **157**:212, 1933.
265. Ochsner, A. J., in discussion on Exophthalmic Goiter, *Tr. Am. S. A.* **23**:162, 1905.

266. Okkels, Harald: Studies on the Thyroid Gland: On the Histology and Cytology of Normal and Abnormal Thyroids in Man, *Acta path. et microbiol. Scandinav.* **9**:1, 1932.
267. Okkels, Harald: Fonctionnement cellulaire et appareil de Golgi; sécrétion rénale et thyroïdienne, *Compt. rend. Soc. de biol.* **112**:1691 (April 1) 1933.
268. Okkels, Harald: The Mechanism of Secretion in the Thyroid Gland, *Acta path. et microbiol. Scandinav.* **16**:303, 1933.
269. Okkels, Harald: Stades nitiaux de la sécrétion thyroïdienne: Les granulations oxydasiques, *Compt. rend. Soc. de biol.* **116**:251 (April 12) 1934.
270. Okkels, H., and Krogh, Marie: Studies on the Thyroid Gland: Stimulation and Inhibition of Rate of Secretion, *Acta path et microbiol. Scandinav.* **10**:118, 1933.
271. Ord, W. M.: On Myxoedema, a Term Proposed to be Applied to an Essential Condition in the "Cretinoid" Affection Occasionally Observed in Middle-Aged Women, *Tr. Med.-Chir. Soc. London* **61**:57, 1878.
272. Oswald, Adolf: Die Eiweisskörper der Schilddrüse, *Ztschr. f. physiol. Chem.* **27**:14, 1899.
273. Oswald, Adolf: Zur Kenntnis des Thyreoglobulins, *Ztschr. f. physiol. Chem.* **32**:121, 1901.
274. Parry, C. H.: Enlargement of the Thyroid Gland in Connection with Enlargement or Palpitation of the Heart, collected unpublished medical writings, 1825, vol. 2, p. 111.
275. Pemberton, J. deJ.: The Surgical Management of Toxic Goiters, *Boston M. & S. J.* **186**:244 (Feb. 23) 1922.
276. Pemberton, J. deJ.: The Rational Treatment of Hyperthyroidism, *South M. J.* **27**:323 (April) 1934.
277. Pemberton, J. deJ., and Haines, S. F.: Hyperfunction of the Thyroid Gland: Recent Developments in Clinical Recognition and Surgical Treatment, *Am. J. Surg.* **23**:399 (March) 1934.
278. Plummer, H. S.: The Function of the Thyroid, Normal and Abnormal, *Tr. A. Am. Physicians* **31**:128, 1916.
279. Plummer, H. S.: Interrelationship of Function of the Thyroid Gland, and of Its Active Agent, Thyroxin, in the Tissues of the Body, *J. A. M. A.* **77**:243 (July 23) 1921.
280. Plummer, H. S.: The Functions of the Normal and Abnormal Thyroid Gland: Histology of the Normal Thyroid, in *Oxford Medicine*, New York, Oxford University Press, 1922, vol. 3, p. 839.
281. Plummer, H. S.: Results of Administering of Iodin to Patients Having Exophthalmic Goiter, *J. A. M. A.* **80**:1955 (June 30) 1923.
282. Plummer, H. S.: The Function of the Thyroid Gland, in Mayo, C. H., and Plummer, H. S.: *The Beaumont Foundation Lectures*, St. Louis, C. V. Mosby Company, 1925, p. 45.
283. Plummer, H. S., and Boothby, W. M.: The Value of Iodin in Exophthalmic Goiter, *Iowa M. Soc. J.* **14**:66 (Feb.) 1924; *Illinois M. J.* **46**:401 (Dec.) 1924; *Collected Papers of Mayo Clinic* **15**:565, 1923.
284. Plummer, H. S.; Wilson, L. B., and Boothby, W. M.: Diseases of the Thyroid Gland, in *Oxford Medicine*, New York, Oxford University Press, 1920, vol. 3, p. 838.
285. Prevost, quoted by St. Lager.
286. De Quervain, F.: The Pathological Physiology of Endemic Thyropathy, in Report of the International Conference on Goiter, August 24 to 26, 1927, Bern, Hans Huber, 1929, p. 124.

287. De Quervain, F.: Der Stand der Kropfbekämpfung in der Schweiz, München. med. Wchnschr. **81**:1020, 1934.
288. Rehn, Louis: Ueber die Extirpation des Kropfs bei Morbus Basedowii, Berl. klin. Wchnschr. **21**:163 (March 17) 1884.
289. Rehn, L.: Die chirurgische Behandlung des Morbus Basedow, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **7**:165, 1901.
290. Reith, J. F. (abstractor): Het Kropvraagstuk in Nederland, Rijksuitgeverij in de Haag, Augustus, 1932.
291. Reith, J. F.: Hohe tägliche Zufuhr von anorganischen Jod durch holländische Leitungswässer, Biochem. Ztschr. **263**:395, 1933.
292. Reith, J. F.: Kropf und Jod in Holland, Schweiz. med. Wchnschr. **63**:791 (Aug. 12) 1933.
293. Report On Myxedema, by a Committee of the Society Nominated Dec. 14, 1883, to Investigate the Subject of Myxedema, Tr. Clin. Soc. London **21**: 298, 1888.
294. Reverdin, M. J. L.: Accidents consécutifs à l'ablation totale du goître, abstr., Rev. méd. de la Suisse **2**:539, 1882.
295. Reverdin, J. L., and Reverdin, August: Note sur vingt-deux operations de goître, Rev. méd. de la Suisse Rom. **3**:169, 233, 309 and 413, 1883.
296. Romanis, W. H. C.: Observations on Exophthalmic Goiter, Brit. M. J. **1**:87 (Jan. 21) 1933.
297. Rubner, Max: Die Gesetze des Energieverbrauchs bei der Ernährung, Leipzig, Franz Deuticke, 1902.
298. St. Lager, J.: Etudes sur les causes du crétinisme et du goître endémique, Paris, J. B. Baillière et fils, 1867.
299. Salter, W. T.; Lerman, J., and Means, J. H.: The Calorigenic Action of d- and l-thyroxin, J. Clin. Investigation **14**:37 (Jan.) 1935.
300. Sandström Ivar: Ueber eine neue Drüse beim Menschen und bei verschiedenen Säugethieren, Hoffmann and Schwalbe's Jahresb., Upsala **9**:114, 1881; Om en ny körtel hos menniskan och åtskilliga däggdjur, Upsala läkaref. förh. **15**:441, 1880.
301. Sauerbruch, F.: Der Morbus Basedow, Arch. f. klin. Chir. **167**:332, 1931.
302. Sauvé, M. L.: Compte rendu des travaux de la Société nationale de chirurgie pendant l'année 1931, Bull. et mém. Soc. nat. de chir. **58**:99 (Jan. 20) 1932.
303. Schiff: Résumé d'une série d'expériences sur les effets de l'ablation des corps thyroïdes, Rev. méd. de la Suisse Rom. **4**:65 and 425, 1884.
304. Schmeckebier, M. M.: Normal and Experimentally Modified Mitotic Activity of Adrenal Gland in Guinea Pig, Proc. Soc. Exper. Biol. & Med. **31**:770 (April) 1934.
305. Schmieden, Viktor, chairman, Symposium on Morbus Basedow, 55 Tagung der Deutschen Gesellschaft für Chirurgie, 1931, Arch. f. klin. Chir. **167**: 79, 1931.
306. Schneider, E.: Die Rolle des Jodes in der Vorbehandlung des Morbus Basedow, Arch. f. klin. Chir. **167**:380, 1931.
307. Schneider, Erich: Concerning the Broadening of the Indications for Operation in Exophthalmic Goitre Through the Recognition at the Bedside of a Secondary Thyrogenic Injury to the Liver, Internat. Clin. **2**:87 (June) 1934.
308. Schneider, E., and Widmann, E.: Klinische und experimentelle Untersuchungen zum Problem des Kropfes und der Basedowschen Krankheit, Deutsche Ztschr. f. Chir. **238**:206 (Dec. 14) 1932.

309. Schneider, E., and Widmann, E.: Klinische und experimentelle Untersuchungen zum Problem des Kropfes und der Basedowschen Krankheit, *Deutsche Ztschr. f. Chir.* **241**:778, 1933.
310. Semon, Felix, in discussion on Drewitt, Dawtrey: *Brit. M. J.* **2**:1072, 1883.
311. Silberberg, Martin: Effects of Combined Administration of Extracts of Anterior Lobe of Pituitary and of Potassium Iodide on Thyroid Gland, *Proc. Soc. Exper. Biol. & Med.* **27**:166 (Dec.) 1929.
312. Siebert, W. J., and Smith, R. S.: Effect of Potassium Iodide on Basal Metabolism in Guinea Pigs, *Proc. Soc. Exper. Biol. & Med.* **27**:629 (April) 1930.
313. Siebert, W. J., and Smith, R. S.: Effect of Various Anterior Pituitary Preparations on Basal Metabolism in Guinea Pigs, *Proc. Soc. Exper. Biol. & Med.* **27**:622 (April) 1930.
314. Siebert, W. J., and Smith, R. S.: The Effect of Various Anterior Pituitary Preparations upon Basal Metabolism in Partially Thyroidectomized and in Completely Thyroidectomized Guinea Pigs, *Am. J. Physiol.* **95**:396 (Nov.) 1930.
315. Siebert, W. J., and Thurston, E. W.: Basal Metabolism after KI with Acid Extract of Anterior Pituitary Glands, Pituitary Tablets and with Thyroid, *Proc. Soc. Exper. Biol. & Med.* **29**:652 (Feb.) 1932.
316. Smith, P. E.: Increased Skeletal Effects in A. P. Growth-Hormone Injections by Administration of Thyroid in Hypophysectomized, Thyro-Parathyroidectomized Rats, *Proc. Soc. Exper. Biol. & Med.* **30**:1252 (June) 1933.
317. Smith, P. E.: General Physiology of the Anterior Hypophysis, *J. A. M. A.* **104**:548 (Feb. 16) 1935.
318. Starlinger, F., and Brücke, H.: Erfahrungen an 290 Basedowkranken der Klinik von Eiselsberg, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **43**:495, 1934.
319. Starr, Paul; Segall, H. N.; Walcott, H. P., and Means, J. H.: The Effect of Iodin in Exophthalmic Goiter, *Arch. Int. Med.* **34**:355 (Sept.) 1924.
320. Thompson, W. O.; Alper, J. M.; Thompson, P. K., and Dickie, L. F. N.: Effect of Diiodotyrosine on Basal Metabolism in Myxedema, *J. Clin. Investigation* **13**:29 (Jan.) 1934.
321. Thompson, W. O.; Brailey, A. G., and Thompson, P. K.: The Effective Range of Iodine Dosage in Exophthalmic Goiter: Preliminary Report, *J. A. M. A.* **91**:1719 (Dec. 1) 1928.
322. Thompson, W. O.; Brailey, A. G.; Thompson, P. K., and Thorpe, E. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: The Effect on Basal Metabolism of Rest and of the Daily Administration of One Drop of Compound Solution of Iodine, *Arch. Int. Med.* **45**:261 (Feb.) 1930.
323. Thompson, W. O.; Taylor, S. G., III, and Meyer, K. A.: Factors Influencing Operative Mortality in Exophthalmic Goiter, *Ann. Int. Med.* **8**:350 (Sept.) 1934.
324. Thompson, W. O.; Taylor, S. G., III; Thompson, P. K., and Dickie, L. F. N.: Calorigenic Action of Extracts of Anterior Lobe of Pituitary, *J. A. M. A.* **104**:252 (Jan. 19) 1935.
325. Thompson, W. O.; Thompson, P. K.; Taylor, S. G., III; Alper, J. M., and Dickie, L. F. N.: The Effects of Various Compounds of Thyroxine on the Basal Metabolism, *Endocrinology* **18**:228 (March-April) 1934.
326. Thompson, W. O.; Thompson, P. K.; Taylor, S. G., III; Nadler, S. B., and Dickie, L. F. N.: The Pharmacology of the Thyroid in Man, *J. A. M. A.* **104**:972 (March 23) 1935.

327. Tillgren, J., and Sundgren, Nils: Hyperthyroidism and Lugol Treatment: IV. Operated Cases, *Acta med. Scandinav.* **83**:391 (Oct.) 1934.
328. Trousseau: Du goître exophthalmique; nouveaux faits cliniques pour servir à l'histoire de cette maladie, *Gaz. d. hôp.* **33**:553, 1860; **37**:109, 1864.
329. Uffenorde, Hellmut: Ueber die Wirkung von jodhaltiger Salinenluft auf Schilddrüsenhyperplasie, *Ztschr. f. d. ges. exper. Med.* **93**:547, 1934.
330. Uhlenhuth, Eduard, and Schwartzbach, Saul: The Morphology and Physiology of the Salamander Thyroid Gland: The Anterior Lobe of the Hypophysis as a Control Mechanism of the Function of the Thyroid Gland, *Brit. J. Exper. Biol.* **5**:1 (Sept.) 1927.
331. Vassale, G., and Generali, F.: Sugli effetti dell' estirpazione delle ghiandole paratiroides, *Riv. di pat. nerv.* **1**:95, 1896.
332. Vassale, G., and Generali, F.: Sur les effets de l'extirpation des glandes parathyroïdes, *Arch. ital. d. biol.* **25**:459, 1896.
333. Vassale, G., and Generali, F.: Sur les effets de l'extirpation des glandes parathyroïdiennes, *Arch. ital. d. biol.* **26**:61, 1896.
334. Wallace, H. L., and Wevill, L. B.: Toxic Goiter: An Analysis of the Results of Surgical Treatment, *Edinburgh M. J.* **40**:598, 1933.
335. Waller, H. E.: On the Value of Iodine, Taken Internally, in Graves' Disease, *Prescriber* **8**:153, 1914.
336. Welch, W. H.: Microscopical Specimens of the Thyroid After Partial Extirpation, *M. News* **53**:455 (Sept. 20) 1888.
337. Wheeler, H. L., and Jamieson, G. S.: Synthesis of Iodogorgoic Acid, *Am. Chem. J.* **33**:365 (April) 1905.
338. Wilder, R. M.: Hyperthyroidism, Myxedema and Diabetes, *Arch. Int. Med.* **38**:736 (Dec.) 1926.
339. Wilson, L. B.: The Pathological Changes in the Thyroid Gland, as Related to the Varying Symptoms in Graves' Disease, *Am. J. M. Sc.* **136**:851, 1908.
340. Wilson, L. B.: The Pathology of the Thyroid in Exophthalmic Goitre, *Tr. A. Am. Physicians* **28**:576, 1913.
341. Wilson, L. B.: A Study of the Pathology of the Thyroids from Cases of Toxic Non-Exophthalmic Goiter, *Am. J. M. Sc.* **147**:344, 1914.
342. Wilson, L. B.: Pathologic Changes in the Muscular and Nervous Systems in Goiter, *Collected Papers of Mayo Clinic*, Philadelphia, W. B. Saunders Company, 1915, vol. 7, p. 438.
343. Wilson, L. B.: The Pathologic Changes in the Sympathetic System in Goiter, *Am. J. M. Sc.* **152**:799 (Nov.) 1916.
344. Wilson, L. B.: The Pathologic Classification of Lesions of the Thyroid Gland, *Ann. Clin. Med.* **1**:44 (July) 1922.
345. Wilson, L. B., and Kendall, E. C.: The Relationship of the Pathologic Histology and the Iodin Compounds of the Human Thyroid, *Am. J. M. Sc.* **151**:79 (Jan.) 1916.
346. Winkenwerder, W. L., and McEachern, Donald: The Use of Iodine in the Preoperative Treatment of Hyperthyroidism; with Remarks on Iodine Remissions as Observed in Baltimore, Maryland, *Bull. Johns Hopkins Hosp.* **51**:282 (Nov.) 1932.
347. Wölfler, Anton: Weitere Beiträge zur chirurgischen Behandlung des Kropfes, *Wien. med. Wchnschr.* **29**:731, 758, 782, 810 and 831, 1879; Zur chirurgischen Behandlung des Kropfes, *Arch. f. klin. Chir.* **24**:157, 1879; Zur Kenntnis und Eintheilung der verschiedenen Formen des gutartigen Kropfes, *Wien. med. Wchnschr.* **33**:1421, 1883.

Book Reviews

The Patient and the Weather. By William F. Petersen. Volume II. **Autonomic Disintegration.** Price, \$6.50. Pp. 530, with 249 figures and charts. Ann Arbor, Mich.: Edwards Brothers, Inc., 1934.

This is the second of a coherent series of five or six monographs on the effect of meteorologic factors on the functioning of organs and the localization of disease. Petersen is professor of pathology and bacteriology of the University of Illinois College of Medicine, Chicago. His present thesis is that cyclonic disturbances, which are especially characteristic of the northern tier of states of the United States, bring about stimulation, overstimulation and fatigue of organs and organ systems and in this manner predispose to the localization of disease. While the meteorologic factor is recognized as being only one of several environmental factors in the "constellation of events" which influence the human mechanism, it probably is the most important. In volume I it was shown that the normal person reacts to his meteorologic environment in a chemical and endocrine rhythm conditioned by the recurrent changes of the environment. In volume II are observations on persons who respond excessively to meteorologic change, "in whom clinical reflections become apparent because the chemical and endocrine tides that are set up are unusual in amplitude or because tissue foci exist which cannot adequately accommodate to even the normal swings of the metabolic rhythm." The volume begins with the discussion of vascular spasm and resultant anoxemia, thus setting the stage for the subsequent presentation of the records of cases in a group of pathologic conditions characterized by special susceptibility to changes in the weather. Thus, in migraine, attacks are shown to occur principally in correlation with "cyclonic interfaces," namely, the period of change from the warm, light, more opaque, moist and more heavily ionized air from the south to the cold, clear, dry and less ionized air of the "polar inflow" which follows the passage of the center of the cyclonic disturbance over the given meridian of latitude; the same is true for attacks of epilepsy, eclampsia, mucous colitis, urticaria, asthma, glaucoma and other syndromes. In cases of peptic ulcer the author shows that gastric episodes (hemorrhage and perforation) occur most often in connection with cyclonic interfaces and are probably predicated on pressor changes, also that the distribution of ulcer according to the draft statistics and the mortality statistics of the United States and Canada, is related to the region of the storm tracks. The process of ulcer formation and subsequent periodic aggravation is pictured as follows: "In the meteorologically induced anoxemic stimulation . . . the mucosa of the stomach participates in a degree that will be greater in the unstable and poorly buffered individual. . . . Hyperacidity is the manifestation of the stimulation of the mucosa and the implication of the great need for proper oxygenation," but spasm follows and more anoxemia results from this. Thus dyskinesia exists. A great demand for oxygen is created in a mucous membrane, with spasm of its nutrient arteries and consequent anoxemia; stimulation of the tissues is augmented by the anoxemia to the stage of fatigue, and death of the tissue follows. This dysfunction of the vascular supply in ulcer has been recognized by other investigators. The feature that Petersen adds is the recognition of the meteorologic basis of the underlying autonomic dysfunction.

The clinical investigation of many cases presented under the different headings is large, involving elaborate data on blood chemistry, with analyses repeated usually every day for long periods. There are also many detailed records of clinical observations. This evidence seems to sustain the author's contentions, but the burden of proof rests with him, and one gets the impression throughout that much is suggested and little actually proved. Thus, periods of meteorologic disturbance

with no corresponding deviations in the blood pressure and blood chemistry factors and no symptoms occur with disturbing frequency in all the illustrative cases, and clinical episodes, the attacks of epilepsy, for instance, appear sometimes in other stages of the cyclonic periods and by no means regularly at the interfaces of the tropical and polar airs. At least so it seems from examination of the complicated graphs. The data are presented for the most part in these graphs, and unfortunately they are constructed so confusedly as to be almost illegible.

Petersen takes strenuous objection to the tendency in medicine to study detail and to neglect the patient as a whole. However, the avoiding of this error, in emulation of Hippocrates, carries with it the danger of becoming satisfied with generalities and less concerned about actual proofs.

A major difficulty in the study of environment is the enormous complexity involved. Physical, chemical and psychic factors are so multiple that their proper evaluation may not be possible with the means at hand today. The effects of the weather, contrary to Petersen's opinion, are not ignored by wise physicians, even by those who consider that their chief responsibility is to arrive at "a definite diagnosis, particularly in acute conditions." It is widely recognized that more exact knowledge of the effect of weather on disease is badly needed, and it can be safely affirmed that the effort of Petersen and his associates to define the importance of meteorology in medicine will be highly commended, whether or not the conclusions will withstand the criticisms that they will provoke.

De Venarum Ostiolis 1603 of Hieronymus Fabricius ab Aquapendente (1533?-1619). Facsimile edition with introduction, translation and notes by K. J. Franklin, D.M., Tutor and Lecturer in Physiology of Oriel College and University Demonstrator of Pharmacology, Oxford. Price, \$3 postpaid. Pp. 104, with 7 figures and 8 plates. Springfield, Ill.: Charles C. Thomas, Publisher, 1933.

The pamphlet on the valves of the heart of twenty-three pages was described as but one of the "remaining pamphlets, and of that large work, which we are compiling on the structure of the animal as a whole" (Fabricius). It is thus but a chapter of a contemplated work on the anatomy of the body which was never completed. Fabricius observed that he noted the valves first in 1574 and demonstrated them to his students, including William Harvey, before he published his account of them in 1603—the year after Harvey left Padua. According to Boyle, Harvey, in a private conversation, confided to him "that when he took notice of the Valves in the Veins of so many several Parts of the Body Towards the Heart, but opposed the passage of the Venal Blood the Contrary way: He was invited to imagine . . . That, since the Blood could not well, because of the interposing Valves, be Sent by the Veins to the Limbs; it should be Sent through the Arteries, and Return through the Veins, whose Valves did not oppose its course that way." Fabricius was not the first to either describe the valves or picture them. He was, however, the first to demonstrate them publicly and describe them in detail. Besides the facsimile with its seven plates and translation, this book contains an account of the life of Fabricius, the early history of work on the venous valves, a description of the anatomic theater of the school of anatomy at Padua and a detailed account of the size of the original pages and plates, besides references. In every respect this book is a worthy Thomas publication and one of paramount interest to medical historians.

Sex Hygiene: What to Teach and How to Teach It. By Alfred Worcester, M.D., Henry K. Oliver Professor of Hygiene, Harvard University. Price, \$2.50. Pp. 136. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

Ten years ago in Boston a dinner was given in honor of Dr. Alfred Worcester because his seventieth birthday was approaching. It was said at the time that he represented as well as any one could a physician who had been a strenuous youth

for seventy years and who always had been a pioneer and a crusader—a pioneer in introducing new methods for being more helpful to humanity and a crusader in attacking fearlessly all abuses within the medical profession. It is not surprising, therefore, that at 79, still young at heart, still a pioneer and still a crusader, he should assemble a book defining his conception of that much abused term “sex hygiene” and describing how, as professor of hygiene at Harvard University, he has found this subject can best be taught.

The volume is a collection of essays illustrating how Dr. Worcester more than thirty years ago first came to feel the need for teaching sex hygiene in schools and colleges and how, step by step, he evolved a method for doing this satisfactorily. Certain persons may not agree with all his views or may believe that much of what he accomplishes depends on his own personality rather than on his methods of teaching. This, however, does not detract from the value of his book, which is a personal work, pretending to do no more than state the author's own ideas on the topics which he discusses. These essays have been collected for the assistance of teachers primarily. Physicians, parents and students will also find the volume worth reading, for it deals with matters pertaining to sex logically and with all the sincerity, honesty and fine idealism of the author.

Rheumaprobleme. Band III. Gesammelte Vorträge gehalten auf dem III. Ärztekursus des Rheuma-Forschungs-Instituts am Landesbad der Rheinprovinz in Aachen. Paper. Price, 5.40 marks. Pp. 95. Leipzig: Georg Thieme, 1934.

Extensive researches on rheumatic diseases are being fostered in various countries through the efforts of national groups and committees. Those carried on in Germany are among the most important. The collected reports of the Third Congress held at the Rheuma-Forschungs-Institut in Aachen are published in this volume, which contains eleven contributions by the following: Aschoff (Freiburg in Breisgau), Edens and Manteufel (Düsseldorf), Grashey and Külbs (Köln), Kreuz (Berlin), Schottmüller (Hamburg) and Krebs, Gehlen, Hennes and Vontz (Aachen). Various phases of rheumatic diseases are discussed, including researches on the etiology of rheumatic myocarditis and the significance of bodily constitution in the production of rheumatic diseases. There are several papers on the therapy of the “specific rheumatic infections,” arthritis, arthrosis, rheumatic diseases of the vertebral column, myalgia and neuralgia by various means: medicinal treatment, roentgen rays and other physical means.

Previous conferences were held in 1928 and 1930, and reports of their agenda appeared in 1929 and 1931.

Revista argentina de cardiologia. A bimonthly journal. Volume I, no. 2. Paper. Price, \$6 per year. Pp. 180. With illustrations and charts. Published under the supervision of the editorial board, Buenos Aires, 1934.

This is the second issue of this journal that was introduced during the current year. This number contains three original articles. The first deals with the optical recording of heart sounds; the second discusses gallop rhythm from the same standpoint, and the third shows the effect that may be produced on the electrocardiogram by suspending the heart in saline solution.

A case is reported, with a discussion of a shifting cardiac rhythm in connection with Cheyne-Stokes' respiration. This is followed by a short discussion of the causes of cyanosis in Ayerza's disease. The remainder of the book is devoted to abstracts of articles from the current literature.

The journal is well printed on an excellent quality of paper, and the illustrations are remarkably clear. It is probable that Spanish is less widely read than it should be. Apparently realizing this fact, the editors have added to each of the articles a summary in French, German and English. This journal should be warmly welcomed into literature on cardiovascular disease.

A Textbook of Biochemistry. Edited by Benjamin Harrow, Ph.D., Associate Professor of Chemistry, the City College, College of the City of New York, and Carl P. Sherwin, M.D., Sc.D., Dr.P.H., LL.D., member of the staff of St. Vincent's Hospital and French Hospital, New York City. Cloth. Price, \$6. Pp. 797, with 52 illustrations. Philadelphia: W. B. Saunders Company, 1935.

Composite textbooks of medicine have become common in this country, but so far as the reviewer knows this is the first textbook of biochemistry to be compiled in this way. The obvious advantage of having experts deal with their special fields seems fulfilled when one finds among the authors of various sections such men as McCollum, Bloor, Drummond, Heidelberger, Luck and many others of equal prestige. The subject matter (too extensive to attempt to review in detail) is, for the most part, well presented, each section being followed by a bibliography of outstanding articles or reviews. While one misses the coherent point of view of a one-man book, one doubts whether any one person could cover the subject so adequately.

Treatment by Diet. By Clifford J. Barborka. Price, \$5. Pp. 615, with 8 illustrations. Philadelphia: J. B. Lippincott Company, 1934.

In this excellent compendium Dr. Barborka seems to have reduced to its simplest terms the subject of treatment by diet. The preliminary matters of diet in health, methods of calculating diets and serving meals and other phases of the subject are presented concisely in forty-two pages. Diseases are divided into those in which diet is of paramount importance, such as diabetes, and those in which it is of varying importance. In each instance, however, there is a brief preliminary statement of the nature of the disease in question and the particular dietetic objectives. This is followed by simple general discussions, and then by many detailed lists of diets.

While the reviewer disagrees with Barborka on small points here and there, all will agree that the general principles brought out are sound. On the whole, this is the most useful "practical" book on diet that the reviewer knows of.

The Heart Visible. By J. Polevski. Price, \$5. Pp. 207, with 122 illustrations. Philadelphia: F. A. Davis Company, 1934.

Disguised behind this preposterous title one finds an excellent discussion of cardiovascular roentgenology. Most of the material is accessible in scattered textbooks on cardiology and roentgenology but, as Polevski points out, there is no short book in English in which the subject is taken up in monographic form. An outstanding feature is the large number of good reproductions of roentgenograms around which the text is built; the exposition is clear and the style pleasant. Perhaps Polevski goes a bit far when he states (preface, p. 4) that "a careful fluoroscopic examination is almost equivalent to dissection in vivo," but, on the other hand, it is only fair to say that most physicians do not fully appreciate the detailed information which can be gleaned from careful roentgen study of the heart and aorta. There are a good bibliography and an index.

Diabetic Manual for Patients. By Henry J. John. Second edition. Price, \$1.50. Pp. 232, with 47 illustrations. St. Louis: C. V. Mosby Company, 1934.

The first edition of this manual appeared in 1928. The *ARCHIVES OF INTERNAL MEDICINE* (42:610 [Oct.] 1928) and the *Journal of the American Medical Association* (91:1928 [Oct. 20] 1928) contained reviews of it, both reviews speaking well of the book. The second edition is a few pages longer than the first and has a few more illustrations. The manual continues to be an intelligent booklet, useful for both diabetic patients and practitioners or students who wish to brush up on practical diabetic therapy. Once again it is pleasant to notice that the author refers to diabetic manuals already in existence as reading matter recommendable to patients.

Archives of Internal Medicine

VOLUME 56

AUGUST 1935

NUMBER 2

PATHOLOGY OF THE VESSELS OF THE PULMONARY CIRCULATION

PART I

O. BRENNER, M.D., M.R.C.P.

Physician for Outpatients and Physician in Charge of the Cardiographic
Department, Queen's Hospital

BIRMINGHAM, ENGLAND

CONTENTS

Anatomic considerations

Normal histology of the pulmonary vessels

Stem of the pulmonary artery

Large branches

Small muscular branches

Arterioles and venules

Capillaries

Veins

Pathologic physiology

Action of drugs: epinephrine, acetylcholine, histamine, pituitary extract and
digitalis

Emphysema

Fibrosis of the lungs

Pleural adhesions

Heart failure

Other functions of the lungs

Diseases of the pulmonary vessels

Historical introduction

Scheme of present investigation

Classification of diseases of the pulmonary vessels

Secondary pulmonary vascular sclerosis

Classification of the conditions

Incidence

Gross appearances

Dilatation

Atherosclerosis

Distribution of sclerosis

In this series of five papers the superior numbers refer to the bibliography which will be published in connection with the last article. The superior letters refer to footnotes.

This work was done in the Cardiac Department and Pathological Laboratories of the Massachusetts General Hospital, during the tenure of a Rockefeller Foundation medical fellowship.

Microscopic changes

Grading of lesions

Stem of the pulmonary artery

Large elastic arteries

Small muscular arteries

Arterioles and venules

Capillaries

Small veins

Large intrapulmonary veins

Main extrapulmonary pulmonary veins

Muscularity of veins

Systemic vessels

Distribution of sclerosis

Changes in the heart

Etiology of secondary sclerosis

Symptoms

Primary pulmonary vascular sclerosis

Incidence

Gross appearances

Microscopic changes

Symptoms

Diagnosis

Pathogenesis

Nature of vascular changes

Relationship to right ventricular hypertrophy

Symptoms

Endarteritis obliterans

Hyperplasia of the intimal elastic tissue

Intimal endothelial proliferation

Hypertrophy of the media

Fibrosis of the media

Syphilis of the pulmonary arteries

Incidence

Morbid anatomy

Microscopic changes

Symptoms

Diagnosis

Treatment

"Ayerza's disease"

Morbid anatomy

Microscopic changes

Symptoms

Comment

Tuberculosis of the pulmonary vessels

Large elastic arteries

Small muscular arteries

Small veins

Large veins

- Rheumatism of the pulmonary arteries
 - Large arteries
 - Medium-sized arteries
 - Small arteries
 - Capillaries and venules
- Septic inflammation of the pulmonary vessels
 - Spread from infective endocarditis of pulmonary valve
 - Invasion from without
 - Arteries
 - Veins
 - Invasion through the vasa vasorum
 - Infection from the lumen
 - From an infected embolus
 - Direct intimal implantation without embolism
- Periarteritis nodosa
- New growth
 - Primary
 - Secondary
 - Tumor embolism
 - Invasion from without
 - Large arteries
 - Small arteries
 - Arterioles and venules
 - Capillaries
 - Small veins
 - Large veins
 - Influence of neoplasm on occurrence of pulmonary arteriosclerosis
- Thrombosis of pulmonary vessels
 - Incidence
 - Stem of pulmonary artery
 - Symptoms
 - Main right and left arteries
 - Symptoms
 - Large intrapulmonary arteries
 - Symptoms
 - Small muscular arteries
 - Arterioles and venules
 - Small veins
 - Etiology
- Aneurysms of the pulmonary artery
 - Traumatic
 - Mycotic
 - Congenital
 - Syphilitic
- Dissecting aneurysms
- Conclusions

The pulmonary circulation is a most vital portion of the circulatory system since through this restricted field must pass all the blood available for the left heart to pump to the various organs of the body, and only there can the essential gaseous interchanges between blood and air occur.

Moreover, the strain of disease of the heart is usually felt first in the pulmonary circuit, and the earliest symptoms of heart failure are referable to it. Yet less is known of the pulmonary circulation than of almost any other part of the circulatory system. The blood pressure in the various parts of the pulmonary circuit, its variation in health and disease and the influence of the vasomotor nerves and drugs in modifying the blood pressure and blood flow, all are practically unknown in man, and even in animals the evidence is fragmentary and often conflicting. This is largely because of the peculiar difficulties even of animal experimentation, since many of the experiments which have been devised so alter the normal conditions which they are intended to elucidate that conclusions drawn from the results are untrustworthy. Comparatively little is known even of pathologico-anatomic changes in the pulmonary circulation in disease, though such knowledge is much easier to obtain, and it is probably a necessary preliminary to the proper understanding of the pathologic physiology of the pulmonary circulation. It was these considerations which prompted the undertaking of the work reported here.

ANATOMIC CONSIDERATIONS

It is frequently said that the circumference of the pulmonary artery in the child is from 1 to 2 mm. greater than that of the aorta, while in the adult it is from 1 to 5 mm. less.¹³⁶ Jores¹³⁸ said that the aorta becomes wider than the pulmonary artery at the age of 40 in the male and at the age of 50 in the female. Others^a have said that even in the adult the pulmonary artery is wider than the aorta. In the series of 100 consecutive autopsies which were investigated for the purposes of this paper, it was possible to find only 15 adults between the ages of 20 and 55 in whom there was no marked macroscopic evidence of sclerosis either in the stem of the pulmonary artery or in the arch of the aorta and in whom none of the factors which are usually thought capable of causing pulmonary arteriosclerosis (except systemic hypertension in 3 cases) was present. Of these 15 patients, there were only 2 in whom the pulmonary artery, 2 cm. above the cusps, was narrower than the aorta at a corresponding level. The statements to the contrary are perhaps due to the fact that cases of aortic atheroma, in which the aorta is frequently dilated, were not excluded.

Parkinson²²⁵ stated that in males the normal circumference of the pulmonary artery is from 7.2 to 9.1 cm., and that of the aorta, from 7 to 8.1 cm., while in females the circumference of the pulmonary artery is from 6.6 to 8.9 cm. and that of the aorta is from 6.4 to 7.6 cm. Crouzon⁶⁶ said that the average circumference of the pulmonary artery is 11 cm. and that of the aorta, 8.5 cm. Clarke⁵⁷ gave from 8.5 to 9 cm. and from 7.7 to 8 cm. as the general circumferences of the pulmonary artery and aorta, respectively.

(a) 57, 66, 225.

Of the 15 patients in the present series there were 6 males, in whom the circumference of the pulmonary artery varied from 7.2 to 8.3 cm. (average, 7.7 cm.), while that of the aorta was from 5.6 to 8.5 cm. (average, 6.6 cm.). In the 9 females the circumference of the pulmonary artery ranged from 5.8 to 9.3 cm. (average, 7 cm.) and that of the aorta, from 5.2 to 7.3 cm (average, 6.3 cm). Though these figures were derived from data too scanty for statistical analysis, it may be stated with confidence that 11 cm., as given by Crouzon for the average circumference of the pulmonary artery, is much too high. In the present series this figure was approached only in cases of obvious marked dilatation of the pulmonary artery, usually associated with sclerosis. In only 1 case (that of a woman of 44) of the 15 cases in which there was no gross pathologic change in the stem of the pulmonary artery or any of the etiologic factors which might cause dilatation of the pulmonary artery did the circumference of the stem of the pulmonary artery exceed 8.3 cm., and in that case it was 9.3 cm. It is clear, then, that normally the stem of the pulmonary artery is a much more capacious vessel than the aorta, its diameter ranging from 85 to 136 per cent (average, 120 per cent) of that of the aorta in the male and from 97 to 136 per cent (average, 116 per cent) in the female.

The right pulmonary artery at the hilus of the lung usually has a slightly greater circumference than the left, and the sum of the circumferences of the two arteries is greater than that of the stem in any individual case. In the 15 normal persons already mentioned the circumference at the hilus ranged from 3.9 to 5.5 cm. (average, 4.5 cm.) in the males and from 3.8 to 4.8 cm. (average, 4.4 cm.) in the females.

Within the lungs⁶² a branch of the pulmonary artery follows each of the larger subdivisions of the bronchi, but in the remote subdivisions the arteries divide more frequently than the bronchi²⁴⁴ and finally end in small vessels lying between the alveoli and partly enclosing their mouths. The capillaries given off by these vessels run over the surface of the alveoli and then join to form venous radicles, which unite to form lobular veins at the proximal ends of the bronchioles. The pulmonary veins, unlike those in the systemic circulation, are less capacious than the corresponding arteries instead of more so. In the present series, when four pulmonary veins entered the left auricle, their circumference ranged from 2.1 to 3.7 cm. in the males and from 1.5 to 3.7 cm. in the females. If the pulmonary veins had been merged into one vessel with a cross-sectional area equal to that of the four pulmonary veins in each case, the circumference of this vessel would have been from 6 to 6.7 cm. (average, 6.3 cm.) in the males and from 4.1 to 7 cm. (average, 5.8 cm.) in the females. The circumference of such a vein would have ranged from 69 to 93 per cent (average, 78 per cent) of the circumference of the stem of the pulmonary artery in the corresponding case. The effect of this relative narrowness of the pulmonary veins is increased by the

fact that they carry not only the blood which enters the lungs through the pulmonary artery but also some of that which enters through the bronchial arteries. Probably the narrowness of the veins contributes to the ease with which "back pressure" and pulmonary congestion are caused in heart disease.

The bronchial arteries arise usually from one of the upper intercostal arteries or directly from the upper part of the descending thoracic aorta. They run with the bronchi and form capillary plexuses in the submucosa as far as the respiratory bronchioles and alveolar ducts. These join venous plexuses in the bronchial walls. Radicles from this plexus in the upper two or three divisions of the bronchi unite to form the bronchial veins, which open into the azygos and intercostal veins and the venae comites of the internal mammary vein ²⁹ and ultimately into the superior vena cava. But the radicles from this plexus in the finer divisions of the bronchi join the pulmonary veins, and the blood is returned to the left auricle. There is some dispute as to whether there is any direct anastomosis between bronchial and pulmonary arteries, though most observers are agreed that there is not, and Berry, Brailsford and Daly ²⁹ were unable to demonstrate in the dog a direct communication between either arteries or veins. Functioning capillary anastomoses, however, undoubtedly exist,³¹ since in isolated perfused lungs a rise in pressure in the bronchial artery causes an increase in flow from both the azygos and the pulmonary vein, while a rise in pressure in either the azygos or the pulmonary vein causes a rise in pressure in both the bronchial and the pulmonary artery. This communication explains the frequency of the development of marked congestion of the bronchi in cases of heart failure at a time when there is little peripheral systemic venous stasis and possibly accounts in part for the hemoptysis which is so common in cases of heart failure. The chief communication between the pulmonary and the bronchial vascular system is by means of the capillaries, the distribution of which overlaps. Thus, the bronchial capillaries supply not only the bronchioles but also the alveolar ducts and even the interalveolar septums, while the pulmonary capillaries supply the aveoli, atria and alveolar ducts and even the respiratory bronchioles. The nutrition of the alveoli beyond the alveolar ducts is chiefly maintained by the pulmonary capillaries, while in the case of the air sacs in the walls of the alveolar ducts and respiratory bronchioles the bronchial capillaries serve a respiratory function. This overlapping is of considerable importance. Thus, ligation of the pulmonary artery or, in man, pulmonary embolism in the absence of infection or heart failure does not cause pulmonary infarction. Again, ligation of the bronchial vessels to one lobe produces no change, but ligation of both pulmonary and bronchial arteries to one lobe causes gangrene of the lung.

Probably the respiratory function of the bronchial circulation is normally of little importance, but it has been suggested that it may assume

NORMAL HISTOLOGY OF THE PULMONARY VESSELS

The pulmonary artery is inserted into the musculature of the right ventricle by a short tube of fibrous tissue which is continuous with the arterial tube and which is called by Gross and Kugel¹²¹ the "annulus" (fig. 1). This consists usually of dense, almost acellular collagenous tissue which stains deep pink with Van Gieson's stain. The fibers usually run longitudinally, though occasionally they are irregular. Often, for 1 mm. or more above the attachment of the cusps, the subintimal

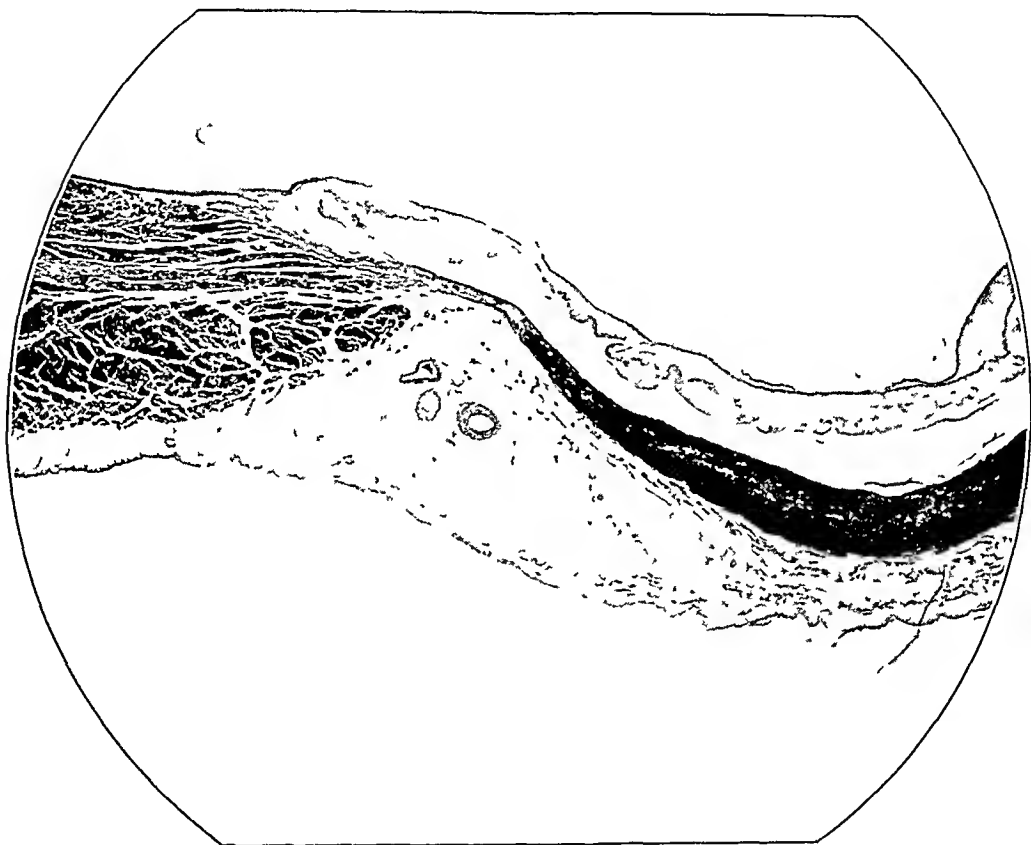


Fig. 1—Photomicrograph of a longitudinal section of the root of the pulmonary artery ($\times 5.5$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). This section shows the beginning of the pulmonary artery, the pulmonary arterial valve and the myocardium of the right ventricle. The darkly stained media of the pulmonary artery ends in a wedge, the apex of which is immediately beneath the endothelium. The more lightly staining annulus is clearly seen, and the loose fibrillar structure of its lower part, continuous with the spongiosa of the cusp of the valve, is shown.

portion of the annulus consists of loosely arranged, delicate, longitudinal fibrils, continuous with similar tissue in the cusps of the valve, called by Gross the "spongiosa" of the valve. Many of these fibrils seem to be the elongated processes of small spindle cells, and they do not give the ordinary reactions of collagen since they stain yellow with Van

Stem of the Pulmonary Artery Above Its Root.—In each case the stem of the pulmonary artery was studied by means of transverse sections taken from a point about 2 cm. above the cusps. It is often said^b that the structure of the pulmonary artery differs only in minor details from that of the aorta. It is true that the general plan of the two vessels is the same, but it is easily possible to distinguish sections of them at a glance.

Intima: Jores¹³⁸ described an elaborate organization of the normal aortic intima in the adult. The deepest layer, the "elastic-muscular longitudinal layer," consists of longitudinal elastic fibers and smooth muscle cells in a collagenous ground-substance. Internal to this is the "hyperplastic layer,"³⁰¹ consisting of circular elastic fibers with some muscle cells. More internally in later life there is a layer of fibrous tissue without muscle or elastic tissue. The whole forms a layer 100 microns or more thick. This characteristic appearance is sometimes missing, the intima being then represented by a thick fibrous layer with more or less elastic tissue and perhaps a few scattered muscle cells.

In the stem of the pulmonary artery (fig. 2) this appearance is not observed. In youth and early adult life the endothelium rests directly on a thick and prominent internal elastic lamina, often seen to be composed of closely packed fibrils usually circularly directed, though some are longitudinal. In later life a thin layer of fibrous tissue often intervenes between the endothelium and the internal elastic lamina, either in the whole extent of the vessel or more commonly only in patches. The normal limit of thickness of this layer was placed at 0.024 mm. by Ljungdahl¹⁷⁶ and at 0.03 mm. by Costa,⁹³ but it is difficult to set a rigid limit since the thickening passes with no sharp line of demarcation into pathologic processes. The connective tissue is dense, is often practically homogeneous and usually stains pink but sometimes brown or a dirty yellow with Van Gieson's stain. It contains a few round, oval and irregular cells and usually in parts of its extent a great deal of fine, poorly staining elastic tissue arranged parallel to the lumen. A layer corresponding to Jores' elastic-muscular longitudinal layer was described by Torhorst,²⁹⁶ separated from the rest of the intima by a strong elastic lamina and distinguished from the underlying media only by the longitudinal direction of its muscular and elastic elements. Ehlers⁹² and Girous¹¹⁴ described a similar layer, unevenly developed, in which, however, many of the elastic and muscular elements were circular or oblique as well as longitudinal. Though the latter observers regarded the layer as part of the media and not of the intima, all three agreed that atheromatous changes in the pulmonary artery usually begin there. Others^c were in agreement with this. Only Hornowski¹³⁶ said that

(b) 63, 138, 296.

(c) 63, 176.

the musculo-elastic longitudinal layer in the pulmonary artery was either absent or so intimately united with the media that it was impossible to separate it.

In the present series in no case was a musculo-elastic longitudinal layer found in the intima, and in most cases nothing resembling it was seen in the media either. In 16 of the 100 patients, however (all but 1, a woman of 26 with congestive heart failure and marked pulmonary

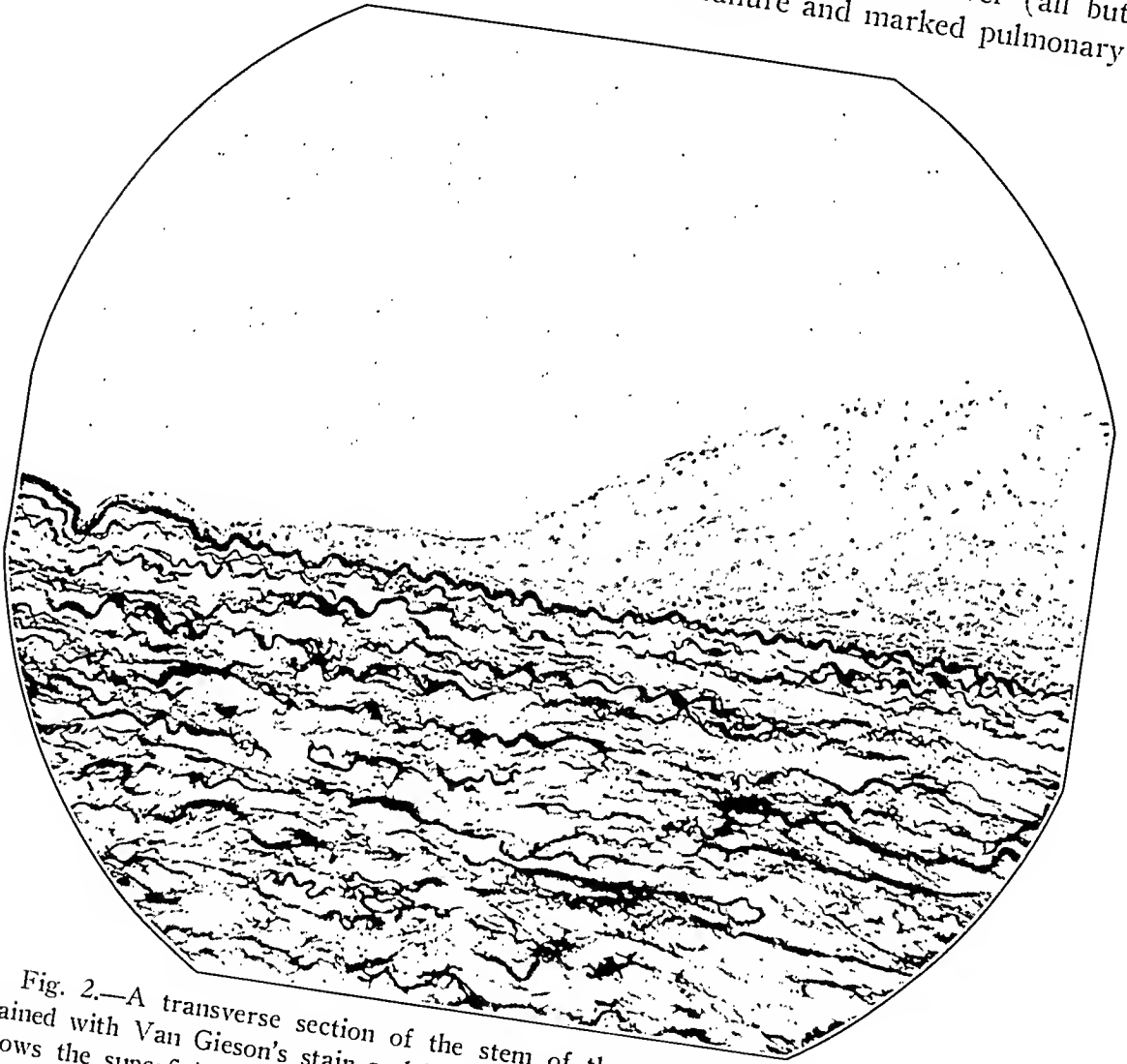


Fig. 2.—A transverse section of the stem of the pulmonary artery ($\times 125$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). This section shows the superficial portion of the media and intima, including a portion of an atheromatous plaque. Below the intima is normal and consists of endothelium directly on the internal elastic lamina. Above this the connective tissue gradually intervenes and develops into an arteriosclerotic patch. The media shows the normal irregularity of the elastic laminae. There is no musculo-elastic longitudinal layer.

vascular sclerosis, over 40), in some parts of the section, but never uniformly, in the superficial 0.05 to 0.07 mm. of the media the elastic membranes were thinner and more widely spaced than elsewhere, and

fine longitudinal elastic fibrils were more numerous than circular fibrils. In this region there was often much dense fibrous tissue, and the scanty muscle cells were often chiefly longitudinally arranged. Marked atheroma of the stem of the pulmonary artery was rather uncommon, but when present, it seemed to be confined to the intima and not to begin in that layer of the media. There is thus nothing in the pulmonary artery which corresponds to the three layers of the aortic intima.

The media is said to be normally from 0.8 to 1.1 mm. thick.^c In the present series in 5 men with a normal pulmonary arterial stem and with none of the conditions usually thought capable of causing pulmonary arteriosclerosis the thickness of the media, with one exception, ranged from 0.647 to 0.797 mm. (average, 0.73 mm.). In the exceptional case the thickness was 1.462 mm. and if that case is included, the average was 0.877 mm. In a similar group of 5 normal women the thickness ranged from 0.553 to 1.115 mm. (average, 0.828 mm.). This is rather less than that found by Costa,⁶³ though the number of cases is too small for certain conclusions to be drawn. The general plan is similar to that of the aorta. In both, the media consists of elastic laminae, muscle and connective tissue, but these elements are somewhat differently arranged. In the aorta the elastic laminae are fairly regular in thickness and closely set. They anastomose by means of thick, oblique side-branches. Fenestrations in the laminae are small and not numerous, since each lamina can be traced for long distances without interruptions, unless its identity is lost by anastomosis with adjacent laminae. There is a great deal of muscle between adjacent laminae, mostly circularly arranged, though with some longitudinal and oblique fibers.

The structure of the pulmonary artery is much more irregular. Its elastic laminae are more scanty and more widely spaced. They are not so parallel, and they are more irregular in shape. In some places they are thin; in others they widen into irregular platelike or clublike expansions. The individual laminae appear short and can be traced only for short distances. They then end, leaving spaces filled by connective tissue, muscle and perhaps a few fine elastic fibrils. Probably this means that the fenestrations are much greater than in the aorta. Between the laminae are many fine irregular fibrils running in all directions. Some of these can be seen connecting adjacent laminae, and perhaps all would be seen to do this if they could be traced far enough. The muscle of the media is usually fairly abundant but is more irregularly arranged than in the aorta. Most of the cells are circularly, but some are longitudinally or obliquely, arranged. Occasionally alternate layers are circular and longitudinal, but usually no such regularity can be made out. Connective tissue is much more abundant than in the aorta. It occurs in large plates, parallel to the lumen, of dense, almost acellular tissue, with fine fibrils, which stain pink with Van Gieson's stain, in a

it is circular, with a few longitudinal or oblique fibers. Connective tissue is much less abundant than in the stem, and in the smallest arteries of this type it is usually confined to a few small patches between the outermost two elastic laminae. In the smaller arteries the elastic laminae are finer, except the innermost and outermost, which are more prominent by contrast.

The adventitia consists of collagenous tissue of varying denseness. Often it consists of short, thick, curved collagenous fibers. There are

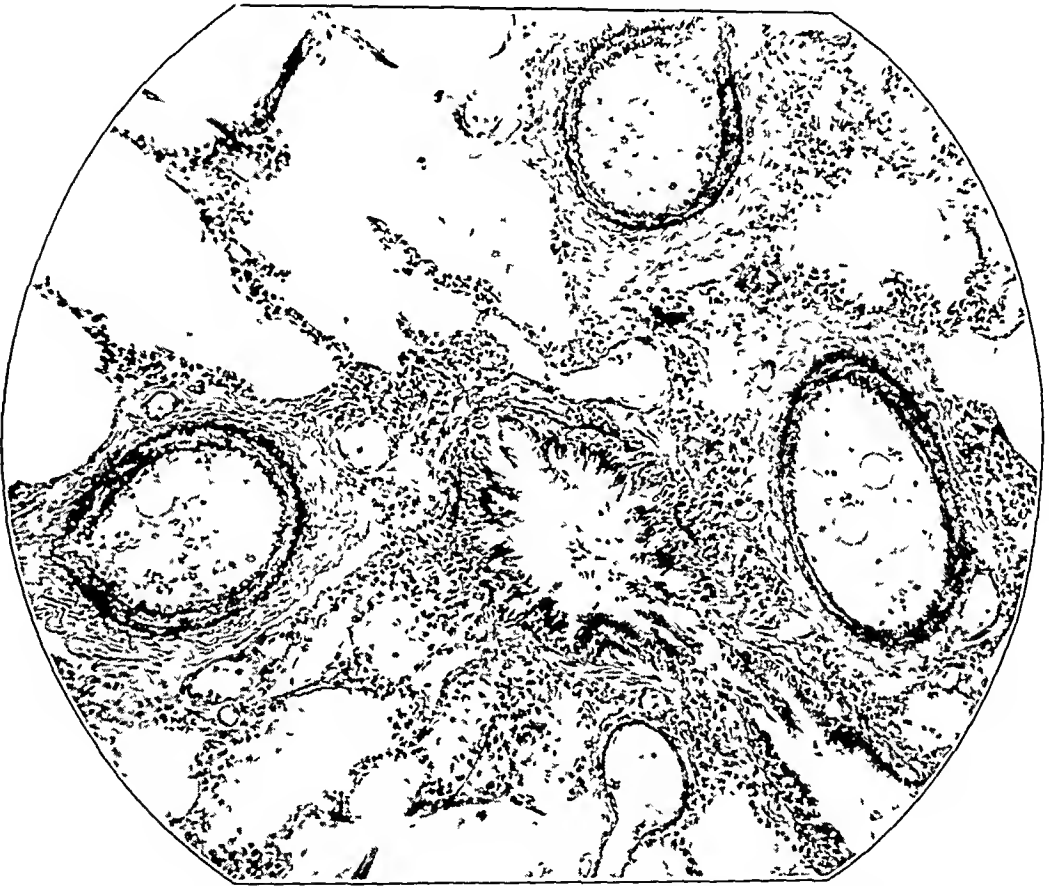


Fig. 3.—Photomicrograph showing three normal small muscular arteries grouped around a small bronchus ($\times 130$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). The media, consisting of a thin layer of muscle between the external and internal elastic laminae, is well shown, as is also the absence of connective tissue between the internal elastic lamina and the intimal endothelium. Below the bronchus is an arteriole or venule, and above it is another. The lower one shows clearly the single fine elastic fibril surrounding the layer of endothelium.

many fine, irregular elastic fibrils, often predominantly longitudinal, and sometimes a few small bundles of longitudinal muscle. There are many blood vessels and nerves, as well as lymphatic vessels, which are well demonstrated when plugged with tumor cells.

difficult to believe that vessels such as these can contract actively and so regulate the pulmonary circulation, as do the systemic arterioles for the systemic circulation; but they seem admirably fitted to follow passively the changes in the pulmonary blood pressure produced in other ways.

Capillaries.—Little need be said of the capillaries except that Krogh and Vimtrup (quoted by Cowdry⁶⁵) stated that they have no Rouget



Fig. 4.—Photomicrograph of a section of a large pulmonary vein ($\times 21$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain) The intima is normal except for a patch of slight thickening over the knuckle near the middle of the lower border. The remainder of the vessel is normal. The irregularity of the elastic tissue of the media is well shown

cells and that it is doubtful if they can contract. But since many observers now think that Rouget cells play no part in capillary contraction, their absence is not proof of an inability to contract.

Veins.—Up to a diameter of from 0.15 to 0.25 mm. the veins have the same structure as the arterioles. Above this the walls gradually thicken, though below an external diameter of 1 mm. the wall still forms

artery. However, in goats⁸⁵ the mean right ventricular pressure remains unaltered during exercise, though the respiratory variations are increased, so that compensatory mechanisms come into play. One of these is that the output of the left heart is also increased, so that more blood is drawn out of the lungs, thus reducing the resistance to the flow of blood.

There is a great deal of evidence that the pulmonary vascular bed can expand and contract as required. Wearn³¹⁴ said that sometimes only one or two capillaries are open on the wall of an alveolus of the living lung, and a little later six or eight are open. Pressure on the abdominal aorta causes many new vessels to open. Schoen²⁷² said that many reserve capillaries at the edge of a living lung watched under the microscope open when the opposite lung is thrown out of action. When the pulmonary veins are clamped, the volume of blood in the lungs is doubled.⁸¹ In the isolated lung perfused under negative pressure respiration an increased flow of blood leads to an increase in the volume of blood in the lungs.⁷⁰ MacGregor¹⁸⁹ found no microscopic change in the caliber of the vessels of the isolated cat's lung perfused at varying rates, though the rate of the flow of blood obviously changed under the influence of drugs, such as epinephrine, and sometimes the flow was actually reversed; but since the resistance to blood flow is proportional to the fourth power of the diameter, a change in diameter too small to be detected microscopically may possibly suffice to initiate great changes in the pressure and flow.

It has long been known that ligature of one pulmonary artery produces no change in the systemic blood pressure or in the output of the left ventricle,³²⁶ and more recently Drinker⁸¹ and Underhill³⁰³ have shown that with the left pulmonary artery tied it is even possible to increase greatly the output of the left ventricle, the right lung freely giving passage to the requisite volume of blood. This is not possible to the same extent when the right pulmonary artery is tied, as apparently the vascular bed in the right lung is more extensive than in the left. When the left pulmonary artery is tied the total volume of the blood in the lungs is unaltered,⁸¹ showing that the vessels in the right lung have dilated so as to accommodate the blood normally held in the left lung. Scarff²⁶⁶ found that ligature of the left pulmonary artery caused a temporary rise of from 30 to 50 per cent in the pulmonary systolic pressure and of from 35 to 100 per cent in the diastolic pressure, and that the pressures returned to normal in from seven to twenty-one days. Even after from three to five months there was no appreciable increase in the size of the heart observed roentgenographically, though at post-mortem examination the right ventricle was found to be slightly heavier. Holman¹³⁴ found that constriction of the stem of the pulmonary artery caused a transient fall in the systemic blood pressure and a rise in pulse

Some authors^a have expressed the belief that the muscle of the small arteries acts as a "peripheral heart" and helps to drive the blood through the lungs. When the resistance to the pulmonary blood flow is increased the muscle of the small pulmonary arteries may hypertrophy (actually this is rare) and so take the strain off the right ventricle. They attempt in this way to explain those cases of emphysema and mitral stenosis without right ventricular hypertrophy. The evidence is flimsy, however, and in Eliaschewitz' case,⁹⁴ which was the most striking, the extra muscle in the pulmonary vessels was longitudinal, and it is difficult to see how this by its contraction could help in the propulsion of the blood.

Little is known of the effect of "back pressure" from the left auricle. The fact that the pulmonary veins are narrower than the arteries would make it easier for pressure from the left auricle to be transmitted back to the pulmonary artery. Berry and Brenner³⁰ in the isolated lung perfused under negative pressure respiration found that a rise in the pulmonary venous pressure caused less than the corresponding rise in the pulmonary arterial pressure and that the volume of blood in the lungs was increased. Thus, the distensibility of the pulmonary vessels prevents the transmission to the pulmonary artery of the full effect of a rise in the left auricular pressure. With the heart-lung preparation Straub found that a rise in systemic blood pressure caused an increase in the left auricular pressure and an increase in the volume of blood in the lungs, but no increase in the pulmonary arterial pressure, thus again showing the importance of the distensibility of the pulmonary vascular bed in sparing the right ventricle.

Anrep,⁷ using the heart-lung preparation, found that a rise in systemic pressure does cause a rise in the pulmonary arterial pressure, but that this is due not to back pressure but to an increased coronary flow, with a resulting more rapid return to, and output by, the right heart. In the intact animal¹⁴⁵ the rise in pulmonary arterial pressure is minimal, as the increased return of blood by the coronary sinus is compensated for by a diminished return by the venae cavae. Berry³¹ showed that sometimes a rise in systemic pressure is accompanied by a fall in pulmonary pressure, possibly owing to local reflexes. Again, if the root of the aorta is compressed¹⁴⁴ there is a rise in the pulmonary arterial pressure owing to the effect of back pressure, but if the abdominal aorta is compressed, the length of aorta proximal to this portion dilates to accommodate more blood, and the rise in pulmonary arterial pressure is slight. In the heart-lung preparation, if a distensible rubber bag is included in the systemic circulation,⁶⁹ a rise in systemic pressure distends the bag, the output of the ventricles diminishes and the pulmonary arterial pressure actually falls. In many cases of systemic hypertension in man the right ventricle as well as the left is hypertrophied, even in

(d) 64, 94, 176, 258.

times dilatation of the stem and extrapulmonary branches of the pulmonary artery. With the intrapulmonary arteries (the smallest used had a circumference of 4 mm.) the response was feeble and dilatation was almost as frequent as contraction. The same was true of the intrapulmonary veins, while with the large extrapulmonary veins, if there was any response, it was always contraction. Gaddum,¹¹¹ using the isolated perfused lung, showed that in the dog epinephrine causes contraction of the arteries and to a less extent of the veins, while after the administration of ergotoxine it causes dilatation of the veins and to a less extent of the arteries. This suggests that the sympathetic system supplies both constrictor and dilator fibers to both pulmonary arterioles and venules but that the supply of constrictor fibers predominates to the former and that the supply of dilator fibers predominates to the latter. In cats small doses of epinephrine cause dilatation of the venules and larger doses, constriction of the arterioles. Berry and Brenner³⁰ found in intact dogs that in its first circulation through the lungs (i. e., before the heart is influenced through the coronary arteries or before the vasomotor or cardioregulatory centers in the medulla are reached) a dose of epinephrine sufficient almost to double the systemic blood pressure slightly accelerates the flow of blood through the lungs, as judged by the sodium cyanide method of Weiss and Robb, suggesting that in the intact animal epinephrine, if anything, slightly dilates the pulmonary vessels. It is known that the final effect of an intravenous injection of epinephrine is to increase the pulmonary blood pressure, but this is due chiefly to the increased output of the right ventricle, possibly aided by an increased coronary blood flow and perhaps by an increased blood flow from the bronchial arteries into the pulmonary capillaries, simulating the effects of back pressure.⁷² At this stage the velocity of the flow of blood through the lungs is markedly increased.

Acetylcholine.—This drug also produces varied results according to the conditions that are present. Franklin,¹⁰⁵ using rings cut from the isolated pulmonary vessels of the dog, found that the main extrapulmonary arteries relaxed, the intrapulmonary arteries gave no response, the intrapulmonary veins contracted more frequently than they relaxed, and the extrapulmonary veins contracted. He concluded, therefore, that since the arteries dilated and the veins contracted, acetylcholine might be expected to cause engorgement of the lungs. Gaddum and Holtz¹¹¹ found in both cats and dogs that acetylcholine in small doses caused a fall and in larger doses a rise in the pulmonary arterial pressure. With such larger doses the effect in cats is exerted on both arterioles and venules, chiefly the latter, while in dogs the main effect is on the arterioles. The changes are abolished by the use of atropine. The authors concluded that with rare exceptions the action of drugs on the pulmonary veins is in the same direction as on the arteries and that

the pulmonary vessels to digitalis, a suggestion which it is certainly difficult to disprove.

Comment.—There is thus much inconclusive evidence that the pulmonary vessels are supplied by vasoconstrictor and dilator nerves and that they react to various drugs. The reactions of both the arteries and the veins may help in regulating the total blood content of the lungs and the distribution of blood within the lungs. But the results of different investigators have been so contradictory that it is difficult to believe that this is an important factor in the regulation of the pulmonary circulation, and the effects in different species vary so greatly that it is not legitimate to transfer any of the results to man. Attempts to study the reactions of the pulmonary vessels in the isolated perfused human lung have failed because of the rapid postmortem autolytic changes, which result in the immediate onset of pulmonary edema when perfusion is begun.³⁰ In man the pulmonary arterioles and venules have no muscle in their walls and consist of a tube of endothelium surrounded by a single elastic fibril. It seems improbable that such vessels could control the pulmonary circulation by their active contractions, though they seem well adapted to follow passively the changes of pressure produced by other means. A slight rise of pulmonary arterial or venous pressure would distend these vessels, so that the rise in pressure would be minimized, while a fall in pressure would cause the vessels to contract passively, thus diminishing the fall. It seems probable, therefore, that the pulmonary circulation is regulated chiefly by the output of the right ventricle and the resistance in the left auricle, modified by the ready distensibility of the small pulmonary vessels, and that independent vasomotor control of the pulmonary vessels plays only a minor part.

The modifications of the physiology of the pulmonary circulation caused by disease are even less understood than the normal physiology.

EMPHYSEMA

The emphysematous chest tends to become fixed in the inspiratory position, so that respiratory movements are limited. The vital capacity is usually reduced and the residual air increased owing to atonic dilatation of the bronchi, so that in spite of the diminished ability to breathe there must be a greater respiratory minute volume to maintain normal alveolar ventilation. The reduction in the respiratory movements diminishes the aid normally given to the pulmonary circulation, throwing a greater load on the right ventricle. Corryllos⁶² said that as in normal inspiration the pulmonary capillaries are dilated and that cyanosis, when present, is due to the free circulation of blood through the incompletely aerated lung. (But Blumgart and Weiss,³¹⁹ who found the vital capacity to be normal in some cases, postulated a physicochemical change in the alveolar

(though Drinker⁸² has demonstrated a diminution of the air content of the lungs after constriction of the pulmonary veins), but the residual air is increased at the expense of the reserve air. Later, pulmonary edema occurs. Modrakowski²⁰⁶ showed in the isolated lung of the cat that a rise in both pulmonary arterial and pulmonary venous pressure is necessary to produce edema. The total volume of the lung is then decreased and the vital capacity still further diminished. Peabody showed that breathing remains comfortable only so long as the tidal air is less than 33 per cent of the vital capacity. The normal tidal air volume may be more than 33 per cent of a reduced vital capacity; the accessory respiratory muscles are brought into play and the patient experiences dyspnea. Harrison showed that diminution in the vital capacity causes a reflex quickening of the respiration¹²⁷ and that a rise in the venous blood pressure has the same effect.¹²⁸ Changes in the blood pressure in the aorta and in the carotid sinuses reflexly affect the rate and depth of respiration, but Heymans¹³² said that changes in the pulmonary circulation have no such effect. However, Dunn⁸⁷ showed that embolism of the pulmonary arterioles causes rapid shallow respirations and that the effect is abolished by section of the vagi. This was confirmed by Moore,²¹⁰ who showed that the effect is not due to distention of the large pulmonary vessels.

In the later stages of heart failure the cardiac output lessens and the systemic venous pressure rises. Changes in the alveolar walls prevent the proper oxygenation of the arterial blood and cyanosis occurs. Deficient oxygenation of the tissues causes an accumulation of lactic acid, and these chemical changes increase the hyperpnea. In these cases failure of the right ventricle, particularly in patients with cardiac asthma, may relieve the subjective distress by diminishing the amount of blood pumped into the lungs and allowing it to accumulate in the liver and other organs.^f

OTHER FUNCTIONS OF THE LUNGS

Aschoff expressed the opinion that the lungs act as a filter and prevent emboli from entering the systemic circulation. Such emboli may originate as thrombi in the systemic veins or they may be pieces of tumor, fat or some other substance. This is borne out by the frequency with which organized thrombi, probably embolic in origin, are found in the small pulmonary vessels (see section on thrombosis of the pulmonary vessels).

Roger²⁵³ expressed the belief that the lungs are active in fat metabolism. After intravenous injection of olive oil in dogs, the fat globules are arrested in the small pulmonary vessels. Only a little passes into

(f) 56, 272, 318.

the systemic circulation. The droplets are then gradually digested by ferments attracted from the lung parenchyma. Oxygen is then necessary, and the process occurs imperfectly when the lung is congested. Roger stated that this process occurs normally in the case of the normal postprandial hyperlipemia, but since after meals the amount of fat in the systemic veins is increased, it seems that much of it is so finely divided that it passes readily through the pulmonary capillaries. MacMahon,¹⁰⁰ in the case of an alcoholic patient with carbon tetrachloride poisoning, found that the blood of the pulmonary artery contained enormous amounts of fat, forming a layer which was 64 per cent of the total on standing. There was no gross fat in other situations, showing that the fat released from the liver had been unable to pass through the pulmonary capillaries.

Eppinger⁹⁸ gave evidence in support of the view that the lungs destroy lactic acid and suggested that the imperfect performance of this function may be of importance in the production of dyspnea in chronic pulmonary disease.

(To be continued)

CARDIOVASCULAR COMPLICATIONS OF TRICHINOSIS

WESLEY W. SPINK, M.D.

BOSTON

In a preliminary report,¹ attention was called to the electrocardiographic changes in a severe case of trichinosis. A fatal case was also reported in which death was due to severe myocarditis and pneumonia. Larvae were recovered from the cardiac muscle by the digestion method described by Augustine and Theiler.² The purpose of this paper is to present the findings in the foregoing cases in more detail, to add the findings in six additional cases and to review briefly the cardiovascular complications of trichinosis.

REPORT OF CASES

The following case is one of severe trichinosis with myocardiac changes as shown in the accompanying electrocardiograms³:

CASE 1.—*History*.—R. K., a 38 year old Jewish housewife, entered the hospital complaining of diarrhea of two weeks' duration. Three weeks before onset she and her daughter had eaten pork chops which were thought to have been well cooked. The daughter had only a mild trichinous infection. The first symptoms presented by the patient (R. K.) were vomiting and diarrhea. There were no abdominal cramps. She had marked loss of appetite and weakness. Three days before admission puffiness of the eyelids developed. There was no edema of the lower extremities. Two days before entry she had severe generalized headache and pain in the muscles of the calves, of the shoulders and of the scapular region.

The past history was unimportant.

Physical Examination.—The patient was well developed and well nourished, quite prostrated, with flushed features, edematous eyelids and chemosis of the conjunctivae. The tongue was coated. The chest was symmetrical, and there was a regular, sighing type of respiration at the rate of 20 per minute. The heart was not enlarged to percussion; the apical impulse was not seen or felt; there were no thrills. Auscultation at the apex revealed the sounds to be distant and muffled. There was a rapid, protodiastolic gallop rhythm. No murmurs were heard, and the pulmonic second sound was equal in loudness to the aortic second sound. The pulse was soft and regular with a rate of 120 per minute. The blood

From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard) of the Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Spink, W. W.: Clinical and Pathological Observations of the Heart in Trichinosis, *J. Clin. Investigation* **13**:708, 1934.

2. Augustine, D. L., and Theiler, H.: Precipitin and Skin Tests as Aids in Diagnosing Trichinosis, *Parasitology* **24**:60, 1932.

3. Dr. Samuel Levine called my attention to the patient.

in figure 1. From that time until the patient was discharged from the hospital, fifty-four days after the onset, her condition gradually improved.

Electrocardiographic and Laboratory Examinations.—Three days after entry to the hospital, or on the seventeenth day of the disease, the first electrocardiogram was made. This is reproduced in figure 2. The significant finding is the inverted

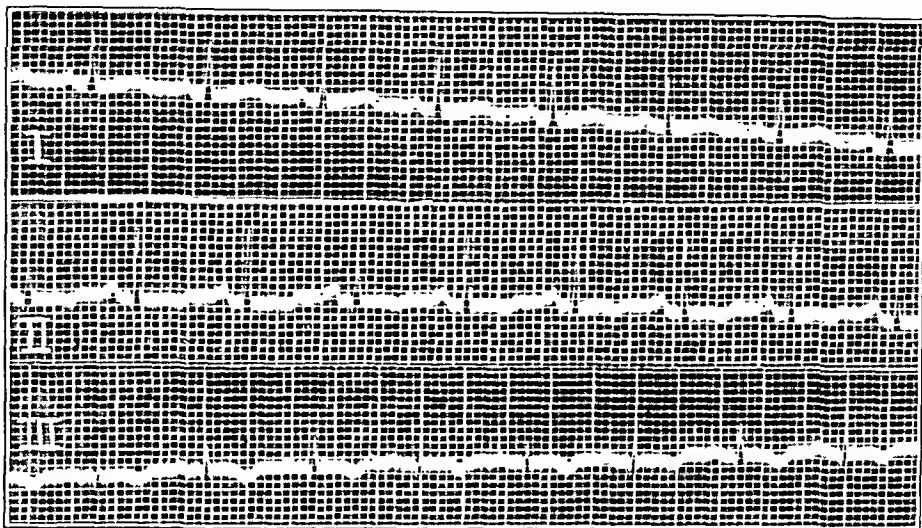


Fig. 2 (case 1).—Electrocardiogram made seventeen days after the onset of trichinosis, showing low amplitude of the T wave in lead I and inversion of the T wave in lead II.

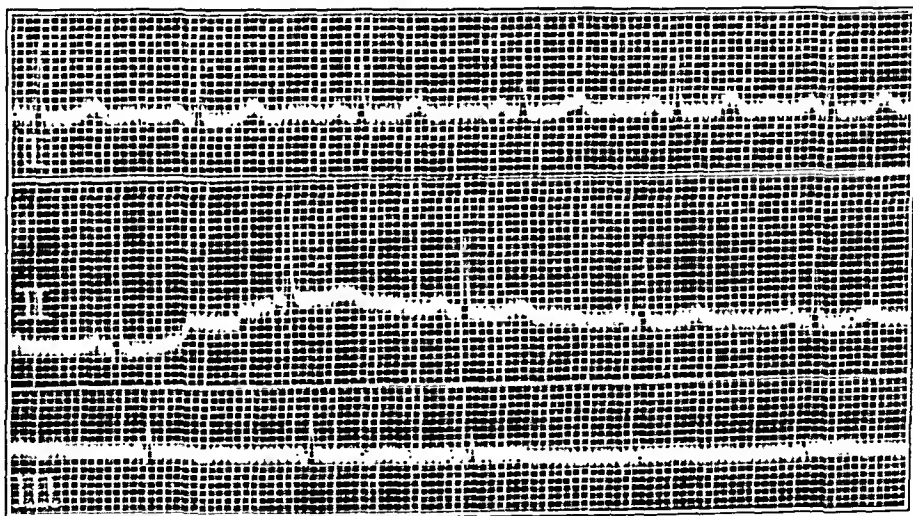


Fig. 3 (case 1).—Electrocardiogram made forty-eight days after the onset of trichinosis, showing increased amplitude of the T wave in leads I and II, with a slight increase in the height of the QRS complex.

T wave with upward convexity in lead II which was considered by Dr. James M. Faulkner as typical of myocardiac disease. Four days later another tracing showed the same changes in the T wave. Forty-nine days after the onset of the disease a normal electrocardiogram was obtained, as shown in figure 3. During

graphic changes she was kept in bed until two successive records were normal. She was discharged, free from symptoms, twenty-six days after the onset of the illness.

Three weeks after discharge her only complaint was that she tired easily. She had no muscular tenderness. An electrocardiogram at that time was normal.

Electrocardiographic and Laboratory Examinations.—Two days after entry an electrocardiogram showed slight sinus arrhythmia. The T wave in lead I was upright; that in lead II, was flat, and those in leads III and IV were inverted. The flat T wave in lead II was considered by Dr. James M. Faulkner as suggestive of myocardiac involvement. Four days later an electrocardiogram was considered normal, with the T wave of lead II upright. Another normal record was obtained two days before discharge.

The urine and stool were normal. The nonprotein nitrogen content of the blood was normal, and the Kahn reaction was negative.

The blood on admission showed 4,900,000 red cells per cubic millimeter, a hemoglobin content of 102 Gm. per hundred cubic centimeters and 18,100 white cells per cubic millimeter with 30 per cent polymorphonuclear eosinophils. The white cell count slowly fell to 9,700 per cubic millimeter with 30 per cent polymorphonuclear eosinophils on the day of discharge from the hospital, the twenty-fifth day of the disease.

The following case illustrates a severe attack of trichinosis complicated by bronchopneumonia and myocarditis, which terminated fatally:

CASE 3.—*History.*—L. T., a 38 year old married Italian laborer, entered the hospital in an incoherent state. He complained of weakness and of pain in the forehead. About eight weeks before entry he obtained some salted pork, and during the following two weeks he ate about 4 pounds (1.8 Kg.) of this meat without cooking it. About three weeks before entry the patient's wife noted that he walked as if he were lame and stiff and that he moved his arms slowly and stiffly. A few days later he complained of pain in the back. That night he went to bed because of chills and fever. A physician who was called stated that the patient had the "grip." The temperature was 102 F. From that time on he remained in bed, took little nourishment and became weaker. Two weeks before entry both eyes "became bloodshot," and a week later the face swelled markedly down to the neck. This lasted about three days and then subsided. The patient had a slight cough, productive of yellow sputum. Two days before entry and following an attack of coughing, he expectorated three mouthfuls of bright red blood. He then became disoriented, suffered from generalized itching and scratched constantly.

Physical Examination.—The patient was well developed and well nourished, disoriented mentally and moderately dyspneic. Examination of the eyes revealed hemorrhages in the lateral aspects of both sclerae, the left being about 2 mm. in diameter and the right, 7 mm. The right fundus had a small fusiform hemorrhage along one of the retinal veins. The lips were dry and cracked; the tongue was dry and coated and the pharynx injected. The heart was of normal size to percussion with a regular rate of 120 per minute. The sounds were of poor quality. However, no abnormal sounds or murmurs were audible. The blood pressure was 90 mm. of mercury systolic and 50 mm. diastolic. On percussion the lungs showed dullness to flatness posteriorly from the midscapular region to the base; tactile fremitus was absent over the same area; the breath sounds and spoken voice were diminished over the scapular region and absent at the base;

crackling râles were heard only over the right midscapular region. The abdomen was tense throughout with no palpable masses and no tenderness. The extremities were normal, but the reflexes were sluggish.

Laboratory Examination.—One blood culture was sterile. The nonprotein nitrogen content of the blood was 75 mg. per hundred cubic centimeters. There were 10,000 white cells per cubic millimeter with 90 per cent polymorphonuclear neutrophils, 5 per cent lymphocytes, 3 per cent polymorphonuclear eosinophils, 1 per cent monocytes and 1 per cent basophils. The red cells and platelets appeared normal. The precipitin test of the blood serum was positive for trichinosis.

Course.—The general condition became progressively worse. The second day after entry the patient became very toxic, cyanotic and restless. Three days after entry he had signs of marked pulmonary congestion and died.

Autopsy (Dr. Edward R. Irgens).—The postmortem examination showed trichinosis, bronchopneumonia of the lower lobes of both lungs, pulmonary edema and congestion, slight cardiac hypertrophy, slight arteriosclerosis of the coronary arteries and aorta and acute tracheobronchitis.

Microscopic examination of the heart (fig. 4) showed that the interstitial connective tissue and connective tissue around the small vessels were infiltrated by polymorphonuclear neutrophils, eosinophils and a few large mononuclear cells. There were scattered necrotic muscle fibers infiltrated by polymorphonuclear neutrophils and eosinophils. No larvae were recognized in several different sections.

After sections for microscopic examination had been taken from the heart, it was carefully washed in running water and then digested in artificial gastric juice. Dr. Donald L. Augustine examined the sediment carefully and found fourteen larvae of *Trichinella spiralis*. These larvae were of the more mature size usually found in skeletal muscle and not of the younger forms found in the circulating blood. This excludes the possibility that they had been present in the blood vessels of the heart.

The fourth case is one of a trichinous infection complicated by right hemiplegia:

CASE 4.—History.—F. M., a 42 year old married Italian woman, presented the symptoms of an infection of the upper respiratory tract. A physician diagnosed the condition as "severe influenza." For four days she was prostrated and feverish. She then showed improvement, but on the seventh day her husband found her in bed, unable to talk or use her right arm or leg. She was subsequently under the care of Dr. Nathan H. Garrick, who called my attention to the case.

Physical Examination.—The patient was a well developed and slightly obese woman with flushed features, dry and cracked lips and flaccid paralysis of the left side of the face. The pharynx was injected. The palatal reflex was not elicited. The heart sounds were rapid, regular and distant; there were no murmurs. The pulse was soft and weak, with a rate of 140 per minute. The blood pressure was 90 mm. of mercury systolic and 50 mm. diastolic. The right arm and leg showed flaccid paralysis. Knee jerks were absent. The biceps reflexes were present and equal. On the right side ankle clonus and Babinski's sign were present.

Course.—The patient's temperature, which was 101 F. at the end of the first week, declined by lysis and became normal a week later. The pulse and respiration likewise returned to normal. The patient slowly improved so that eleven weeks after the onset of the illness she was able to walk. There remained, however, right hemiplegia and paralysis of the left side of the face.

Laboratory Examination.—On the eighth day of the illness the cerebrospinal fluid was normal. The white blood cells numbered 15,500 per cubic millimeter, with 85 per cent polymorphonuclear neutrophils and no eosinophils. The erythrocyte count and hemoglobin content were normal. One week later leukocytosis was still present, but there were 12 per cent polymorphonuclear eosinophils. At the end of three weeks the percentage of eosinophils had risen to 42. The patient was thought to have trichinosis, and seven weeks after the onset the cutaneous and

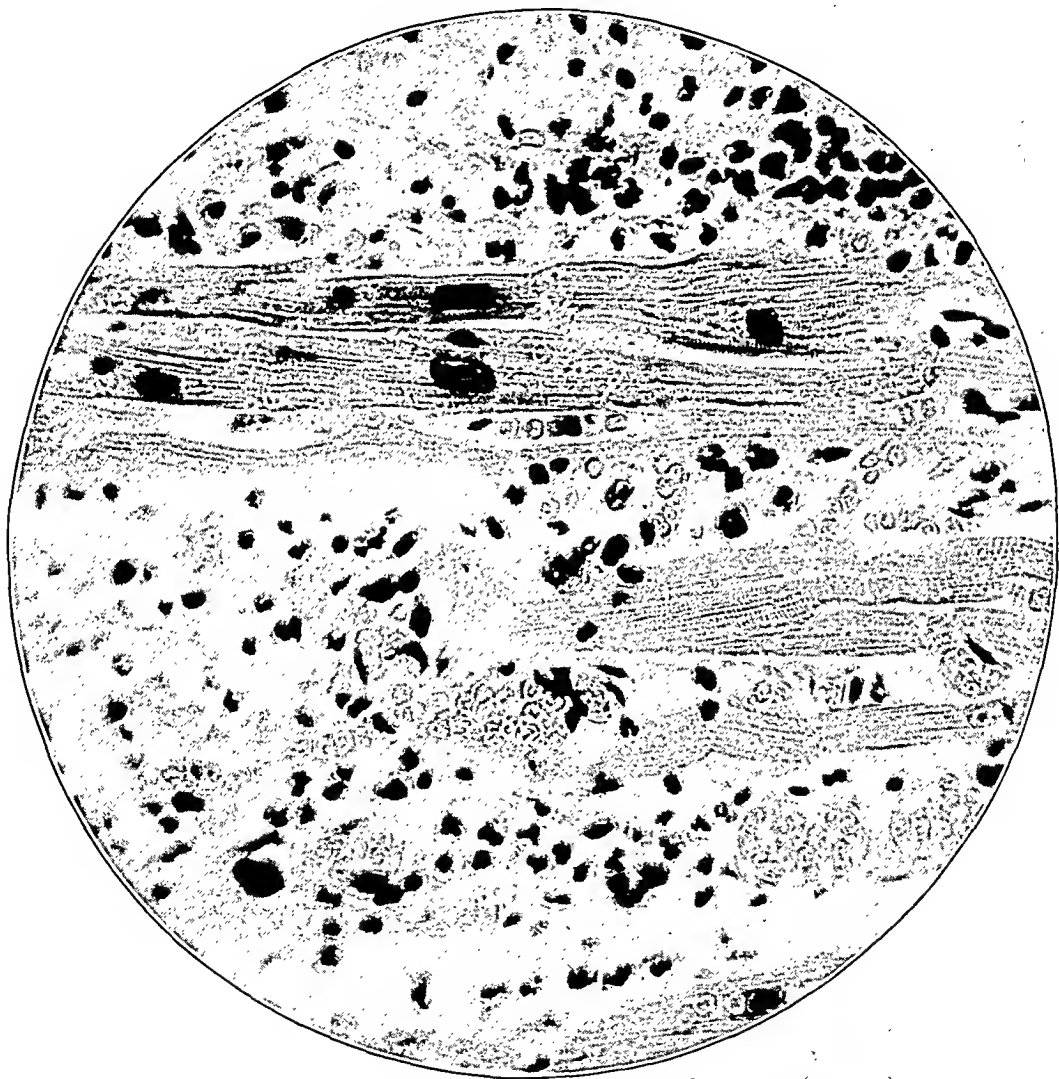


Fig. 4 (case 3).—Photomicrograph of the cardiac muscle, showing necrotic muscle fibers infiltrated by leukocytes, but no trichina larvae ($\times 48$).

precipitin tests for trichinosis were strongly positive. An electrocardiogram made five weeks after the onset showed tachycardia and left axis deviation. Roentgen examination of the heart showed slight enlargement.

Electrocardiographic Findings in Additional Cases.—I had observed twenty-six cases of trichinosis before the patient in case 1 was seen. Because of the findings in case 1 clinical data obtained in the preceding

day of the infection. After that time it became more difficult to find them. Graham's observations were confirmed by Zoller,¹² who worked with guinea-pigs. He observed that after the second week of infection larvae were rarely found in the myocardium. Zoller concluded with Graham that either the larvae were killed in situ or left the myocardium rapidly and entered the circulation again. Zoller expressed a belief that the damage to the cardiac muscle was only temporary, as he found no evidence of permanent alteration of myocardiac tissue.

From the foregoing observations, it seems that there is a definite etiologic relationship between the presence of larvae in the myocardium and myocarditis. However, as late as 1919 Simmonds¹³ was unable to find the larvae in cardiac muscle, and he stated that the damage to the myocardium was due to toxic substances from the trichinae carried by the blood to the heart. It appears from the recent work of Dunlap and Weller¹⁴ "that it is the presence of the larvae in the myocardium and their active migration and not a blood-borne toxic substance which produces the characteristic myocarditis." Their first evidence was that in a series of white rats infected with *T. spiralis*; myocardiac changes with the larvae present in the muscle were found as early as five days after infection and for some time thereafter. Their second evidence was that as soon as active migration of the larvae ceased myocardiac changes were not observed even though encystment of larvae in the skeletal muscle occurred to a marked degree. Myocarditis of toxic origin would not have subsided at this stage.

The histologic picture of myocarditis occurring in trichinosis is not specific. Whereas Cohnheim originally described the lesion as one of parenchymatous degeneration, subsequent investigators have shown that the process is an active, cellular infiltration, usually focal but distributed throughout the myocardium with the production of necrotic and fragmented fibers. Small hemorrhages may be present in the cardiac tissue in the earlier stages. It is to be recalled that Cohnheim's autopsy was performed on a partially decomposed cadaver. In experiments on animals myocarditis may occur as early as the fifth day of infection¹⁴ or as late as the fifteenth day.¹² The cellular response in human cases is for the most part that of the lymphocytic series. Occasionally eosinophils predominate in the inflammatory process. Leukocytes appear to play only a slight rôle, as there are seldom more than a few present. A review of the reports of cases in which the patient died of a com-

12. Zoller, H.: Ueber die Herzmuskelentzündung im Verlauf der Trichinose, *Virchows Arch. f. path. Anat.* **265**:430, 1927.

13. Simmonds, M.: Ueber Myocarditis trichinosa, *Centralbl. f. allg. Path. u. path. Anat.* **30**:1, 1919.

14. Dunlap, G. L., and Weller, C. V.: Pathogenesis of Trichinous Myocarditis, *Proc. Soc. Exper. Biol. & Med.* **30**:1261, 1933.

young man in whom left hemiparesis developed in the eighth week of the disease and who died in a convulsive state. At autopsy there was an excessive vacuolation of brain tissue, caused principally by the enormous amount of enlarged perivascular spaces.

Master and Jaffe ²¹ recently reported the electrocardiographic changes in four cases of trichinosis. Taking an average number of eight records in their four cases, they found that 50 per cent showed tachycardia, 25 per cent showed a prolonged P R interval (0.22 second maximum) and 33 per cent showed inversion of the T wave.

I have observed thirty-five sporadic cases of trichinosis in the past three years. Electrocardiograms were obtained in eighteen of the cases. Abnormal electrocardiographic changes were noted in six (33.3 per cent) of these cases, the ones reported in this study. The earliest changes were observed in the second week of the disease. Only one case presented clinical evidence of myocardiac damage. The electrocardiographic evidences of myocardiac disease in trichinosis are the changes in the T wave and the low amplitude of the Q R S complex. The conducting mechanism may also be affected, as shown by the presence of intraventricular block in one of the cases. These findings demonstrate the importance of close observation for cardiac changes in *severe cases of trichinosis*.

The finding of larvae in digested cardiac tissue confirms the observations of other investigators that the invasion of the myocardium by the parasite appears to be closely related to myocarditis.

It is difficult to draw any definite conclusions in regard to the patient in whom right hemiplegia occurred during the course of a trichinous infection. However, since thromboses and infarctions were reported to have occurred in patients with trichinosis and since the parasite is known to have invaded the brain, there is a possibility of a direct relationship between the trichinosis and the hemiplegia.

SUMMARY

Acute myocarditis occurring in trichinosis may be a nonspecific inflammatory reaction due to the invasion of the myocardium by larvae.

A review of the literature shows that other cardiovascular manifestations include congestion and hemorrhage of the eyes, lungs and gastro-intestinal tract; edema; thrombosis; embolism with infarction, and hypotension.

Six of eighteen cases of trichinosis (33.3 per cent) showed electrocardiographic changes. These changes included an initial flattening or

21. Master, A. M., and Jaffe, H.: Electrocardiographic Evidence of Cardiac Involvement in Acute Disease, *Proc. Soc. Exper. Biol. & Med.* **31**:931, 1934.

inversion of the T wave, especially in lead II, the wave subsequently becoming upright; low amplitude of the QRS complex, and intraventricular block.

The postmortem changes in a fatal case of trichinosis with myocarditis are presented. Another case is recorded in which trichinosis was complicated by a permanent right hemiplegia.

OBSTRUCTING PERICARDITIS

EFFECT OF RESECTION OF THE PERICARDIUM ON THE CIRCULATION OF A PATIENT WITH CONCRETIO CORDIS

C. SIDNEY BURWELL, M.D.

AND

D. FLICKINGER, M.D.

NASHVILLE, TENN.

The symptoms and signs of concretio cordis as a type of obstructing pericarditis were clearly described by Volhard and Schmieden¹ in 1923. They measured the venous pressure and found that it was elevated. Beck and Griswold² in 1930 were able to produce in dogs constricting pericardial scars associated with an elevated venous pressure, a diminished cardiac output, a small pulse and edema. Resection of these scars was followed by a fall in the venous pressure, a rise in the cardiac output and a diminution in the edema.

Burwell and Strayhorn³ in 1932 reported quantitative studies of the circulation in a young man subsequently proved to have concretio cordis. He exhibited a high venous pressure, a small pulse pressure and a diminished cardiac output per minute and per beat. Exercise was associated with an increase in the arteriovenous oxygen difference; but no increase occurred in the output per beat. These studies seem to indicate that the essential defect in the circulatory mechanism was failure of the heart to relax to a normal extent. This patient died suddenly following a resection of the pericardium. Another patient who had previously been successfully treated by operation for a similar condition of the pericardium exhibited venous pressure, pulse pressure and cardiac output within normal limits.

In 1934 Maltby⁴ reported determinations of the output of the heart in three patients with obstructing pericarditis. The cases were

From the Department of Medicine of the Vanderbilt University School of Medicine.

1. Volhard and Schmieden: Ueber Erkennung und Behandlung der Umklammerung des Herzens durch schwierige Perikarditis, *Klin. Wchnschr.* **2**:5 (Jan. 1) 1923.

2. Beck, C. S., and Griswold, R. A.: Pericardiectomy in the Treatment of the Pick Syndrome, *Arch. Surg.* **21**:1064 (Dec.) 1930.

3. Burwell, C. Sidney, and Strayhorn, W. David: Concretio Cordis: I. A Clinical Study, with Observations on the Venous Pressure and Cardiac Output, *Arch. Surg.* **24**:106 (Jan.) 1932.

4. Maltby, Alice B.: Cardiac Output in the Pick Syndrome, *Proc. Soc. Exper. Biol. & Med.* **31**:853 (April) 1934.

The abdomen was distended, and the signs of a large amount of ascites were present. The edge of the liver was felt 10 cm. below the right costal margin in the midclavicular line. Rectal examination revealed no hemorrhoids. The extremities showed wasting and distention of the veins but no demonstrable edema.

The urine showed a trace of albumin, a moderate number of leukocytes and a few hyaline casts. The blood contained 4,200,000 red cells and 10,900 white cells per cubic millimeter and 11 Gm. of hemoglobin per hundred cubic centimeters. The Wassermann and Kahn reactions were negative. A roentgenogram of the chest revealed only a slight enlargement of the cardiac shadow on both sides. There appeared to be fluid at the base of the right lung and thickened pleura at that of the left. Fluoroscopic examination revealed no visible pulsation of the heart and no shift with change in position of the body. The electrocardiogram showed sinus tachycardia, an inverted T wave in all leads and no shift of the electrical axis with changes in the position of the patient.

The venous pressure was 385 mm. of salt solution in the femoral vein and 350 mm. in the median basilic vein.

The patient thus exhibited the classic combination of a high degree of venous congestion with a relatively small, fixed heart. Moreover, there was no evidence of valvular disease, there was no hypertension, the pulse pressure was low and the pulse was paradoxical. A diagnosis of obstructing pericarditis was made. On the basis of experience with similar cases it was believed that tuberculosis was probably the cause of the pericarditis.

During the first week of the patient's stay in the hospital the abdomen was tapped twice, and over 6 liters of greenish-yellow hazy fluid was obtained. The fluid had a specific gravity of 0.019 and contained 500 cells per cubic millimeter. Smears and cultures revealed no bacteria, and a guinea-pig inoculated with the fluid remained well. The patient's heart rate continued to be elevated and was usually between 110 and 140. The temperature varied from 99 to 101 F. The condition remained practically unchanged for seven weeks. During this period the abdomen required tapping on four occasions, yielding a total of 20 liters of fluid. The paradoxical quality of the pulse continued.

During this time fever was present regularly in the evening, the temperature usually reaching 101 F. This fever was believed to be due to an active pericarditis. The activity of the pericardial infection was for many weeks accepted as a sufficient contraindication to operation. During this period, however, the patient gained no ground; there was, aside from the fever, little evidence of intoxication, and the severe discomforts and disabilities were based on the obstruction rather than on the inflammation in the pericardium. It was therefore decided, after this period of observation, that relief of the pericardial obstruction was necessary.

Accordingly, on Nov. 29, 1934, an operative attack on the pericardium was carried out by Dr. Alfred Blalock. A greatly thickened and inextensible pericardium was revealed, the maximum thickness of the parietal layer being 7 mm. Several encapsulated accumulations of purulent fluid were encountered, amounting to about 25 cc. in all. (Culture from this fluid gave a pure culture of *Staphylococcus aureus*.) The character and relations of the thickened pericardium are shown in figure 1. A large part of the anterior portion of this thickened pericardium was resected. Following this resection the pulsation of the heart increased visibly in amplitude.

The resected portions of the pericardium were composed of tough cartilaginous-feeling fibrous tissue. Microscopic examination showed fibrous tissue with diffuse leukocytic infiltration and focal collections of round cells. In certain areas there

were great numbers of polymorphonuclear leukocytes. There was no evidence of tuberculosis. With the Goodpasture stain many cocci could be seen in the granulation tissue on the cardiac side of the pericardium.

Following this operation there was an immediate improvement in the patient's condition. The liver became smaller; the veins of the neck appeared less distended, and the venous pressure was about 100 mm. lower than before operation. Nine days after operation many of the original symptoms and signs reappeared; the liver increased in size, and fluid accumulated in the abdomen. At this time

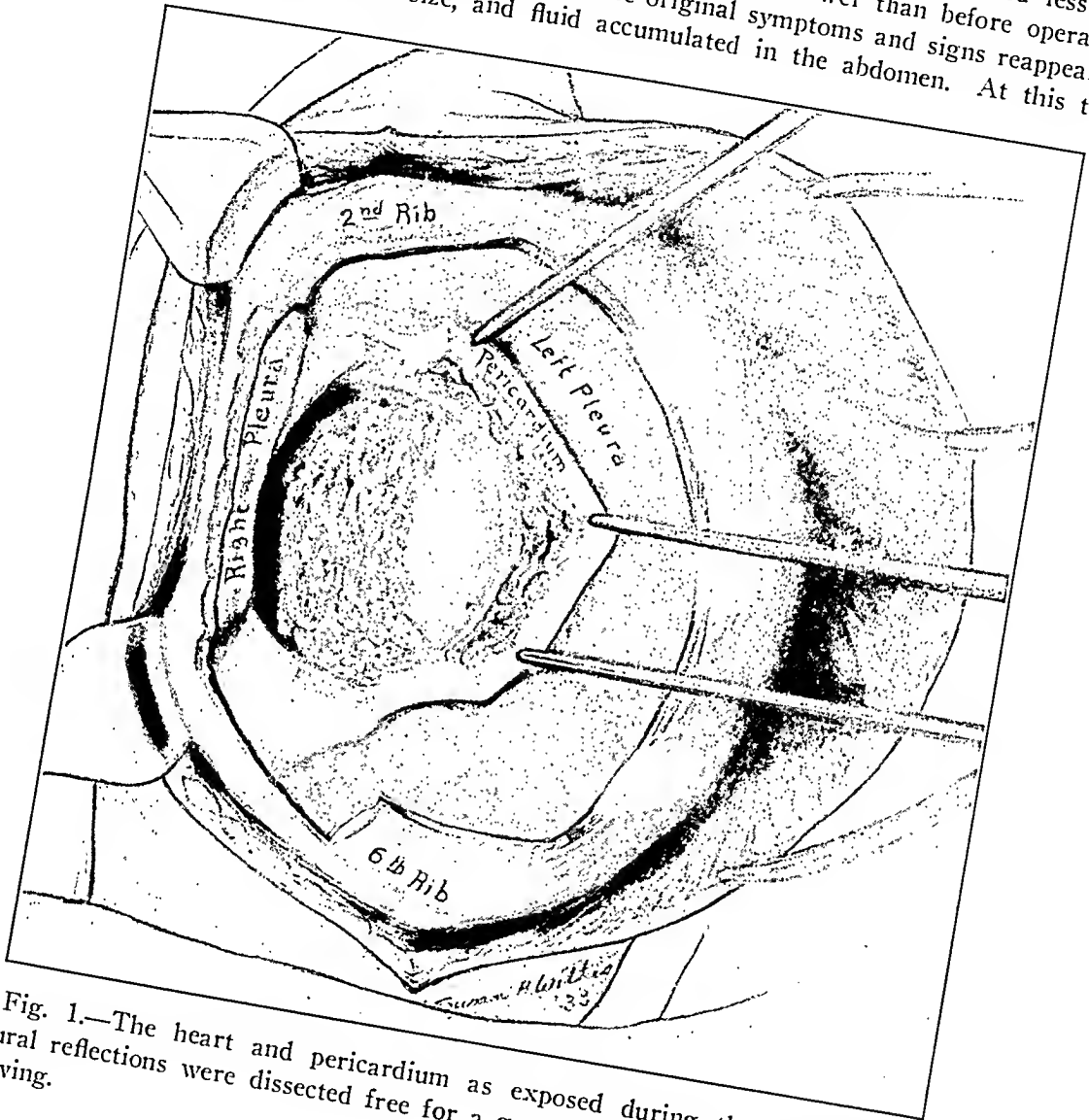


Fig. 1.—The heart and pericardium as exposed during the operation. The pleural reflections were dissected free for a greater distance than is shown in the drawing.

also there was evidence of a massive pleural effusion on the left. Some regression of the symptoms was obtained by thoracentesis with removal of a transudate. For ten days after this the patient exhibited the same signs and a venous pressure of over 300 mm. There was then a gradual change for the better, with an ultimate disappearance in the signs of congestion and a fall in the venous pressure. Five months after admission and three and a half months after the operation the patient was permitted to leave the hospital. At that time he was able to be up all day without signs or symptoms indicative of obstruction to the entry of blood into the heart. Only the final venous

pressure reading of 200 mm. of water indicated that some obstruction was still present. Fluoroscopic examination at that time revealed a cardiac pulsation of approximately normal extent.

His subsequent course was one of continual slow improvement. When last seen (July 9, 1934) he was able to sleep lying flat in bed and to walk 3 miles (4,828 meters) without undue fatigue. Signs of congestion were absent, and the venous pressure as measured on the arm was 125 mm. of saline solution.

NOTE.—On a subsequent visit (Oct. 15, 1934) he reported that he could do moderately vigorous physical work without distress. The venous pressure at this time was 118 mm.

STUDIES IN VENOUS PRESSURE

The venous pressure was studied by the direct method of Moritz and Tabora,⁶ using a syringe with a side-arm as suggested by Griffith,

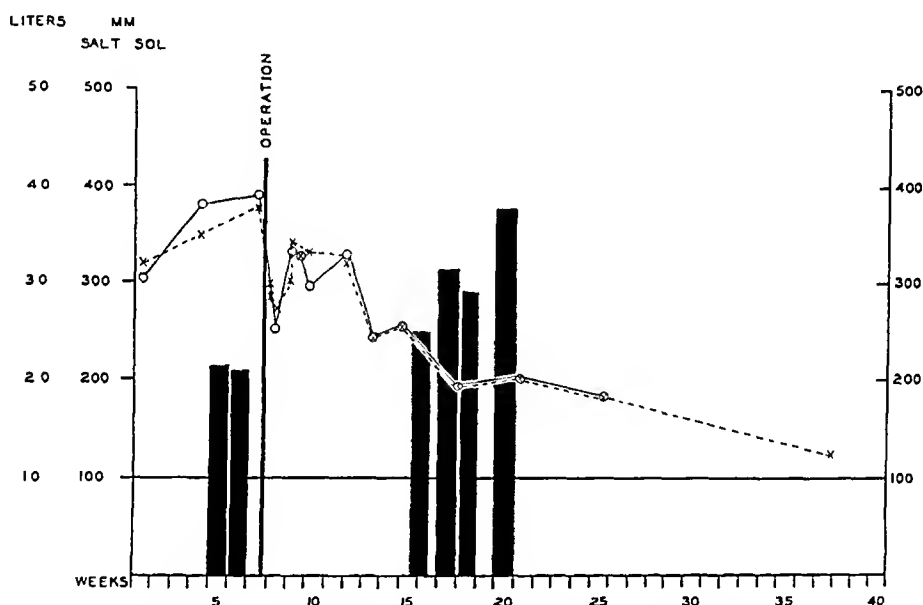


Fig. 2.—Graphic representation of the changes in venous pressure and cardiac output during the period of observation and treatment. The black columns denote the cardiac output per minute. The femoral and cubital venous pressures are designated by circles and crosses, respectively.

Chamberlain and Kitchell.⁷ Observations were made frequently during the patient's stay in the hospital. Because it was considered possible that there might be a difference in the degree of obstruction of the superior and that of the inferior vena cava, measurements were made on the veins of both the arm and the leg. In general, the differences observed were slight, and it was concluded that there was no great

6. Moritz, F., and von Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch. f. klin. Med.* **98**:475, 1910.

7. Griffith, George C.; Chamberlain, C. T., and Kitchell, J. R.: A Simplified Apparatus for Direct Venous Pressure Determination Modified from Moritz and Tabora, *Am. J. M. Sc.* **187**:371 (March) 1934.

arteriovenous difference, between 72 and 92 cc. per liter. The last observations, made several weeks before the patient's discharge, showed a cardiac output of 3.8 liters and an arteriovenous difference of 72 cc. These figures are within the limits of normal. Even the output per beat increased and reached 35 cc.

As is shown in figure 2, the cardiac output rose as the venous pressure fell and as the patient's strength and comfort increased.

COMMENT

Such a diminution in total cardiac output as this patient exhibited may be expected to lead to weakness and fatigability. The small output per beat cannot be increased in this condition,³ and this limitation may be expected to lead to tachycardia, a low pulse pressure and a limited tolerance for exercise. The diminution in cardiac output is thus an important factor in the production of symptoms in patients who suffer from obstructing pericarditis.

The increase in venous pressure is obviously another important factor in the production of symptoms. Aside from the changes in cardiac output a sufficient increase in venous pressure can lead to venous distention, to engorgement of the liver, to the formation of peripheral edema and to the transudation of fluid into the peritoneal and pleural cavities. In this patient changes in the size of the liver and in the rate of formation of ascites were related to changes in the venous pressure.

The importance of differentiating cases of pericardial disease with incomplete filling of the heart from cases of heart failure with incomplete emptying is obvious; therapeutic procedures which are useful in the one may be useless or injurious in the other. The differences and similarities which exist between the manifestations of the two conditions are found to depend on differences and similarities in the dynamics of the circulation in the two instances.

It has been shown that patients with *concretio cordis* exhibit a diminished cardiac output per minute and per beat, a fixed output per beat, a small pulse pressure and venous congestion with high venous pressure. Evidence of comparable diminution in cardiac output and in blood pressure is observed in various forms of acute circulatory collapse (including the forms associated with syncope, with hemorrhagic shock, with severe tachycardia and with coronary occlusion), but diminution of such a degree is rare in and not essential to congestive heart failure, the result of chronic cardiac disease.¹⁰ Comparable venous congestion and comparable elevation of systemic venous pressure are

10. Friedman, Ben; Clark, Gurney; Resnik, Harry, Jr., and Harrison, T. R.: The Effect of Digitalis on the Cardiac Output of Persons with Congestive Heart Failure, *Arch. Int. Med.*, to be published.

PULMONARY TUBERCULOSIS OF THE LOWER LOBE

DAVID REISNER, M.D.

NEW YORK

The question concerning the nature and location of the incipient changes in reinfection forms of pulmonary tuberculosis has enjoyed renewed interest in recent years. There has been considerable discussion on the subject of subapical versus apical location of the early manifestations. The importance of the infraclavicular infiltrations and their significance as precursors of manifest and progressive phthisis has been especially stressed by the German school. It is not intended here to dilate further on this point, which has been so thoroughly discussed by numerous writers. Suffice it to state that the results of these investigations definitely indicate that in a large proportion of the clinically manifest forms the earliest changes are situated outside the apex of the lung.

The interest in the subject presented in this paper was originally aroused by a group of cases in which the location of the changes is frequently considered as atypical for adult forms of pulmonary tuberculosis. Such forms, while by no means common, are nevertheless not infrequently encountered, if one has an opportunity to study a large number of patients with pulmonary tuberculosis. I refer to those instances in which the involvement is found in the midfield of the lung close to the structures of the root. Because of their apparent proximity to the hilar area on the roentgenogram, these lesions are variously referred to as hilus, perihilar or parahilar forms of pulmonary tuberculosis. From such roentgen findings the inference has frequently been drawn that there exists an anatomic relation of these forms with the structures of the root, such as extension of the pathologic process by contiguity from the tracheobronchial lymph nodes into the lung, retrograde infection by way of the lymph vessels or perforation of a caseated lymph node into the bronchial tree with subsequent involvement of the lung. It has been suggested that lesions of this character represent a pathogenetic and clinical entity which is distinct from the usual mode of involvement in the majority of adult forms of pulmonary tuberculosis, and it is thought that they exhibit certain similarities with the childhood

From the Department of Tuberculosis of the Metropolitan Hospital, New York, and the Sea View Hospital, Staten Island, N. Y. (Dr. George G. Ornstein, Director).

forms. Such views have been advocated by a number of authors, more recently by Alexander,¹ Bernard,² Bernard, Lelong and Renard³ and Faber.⁴

However, at no time could such modes of infection as have just been outlined be reconciled with actual anatomic findings. There has been a decided opposition on the part of pathologists to accepting these views. Ghon,⁵ Ghon and Kudlich,⁶ Graeff and Kuepferle⁷ and Tendeloo⁸ have been emphatic in stressing the complete lack of evidence in favor of such conceptions. According to Graeff and Kuepferle, the apparent discrepancies between the anatomic and roentgen findings are merely the result of the superimposition of densities located in various planes of the thoracic cavity. A few clinical observers have likewise called attention to such pitfalls in the interpretation of roentgen findings, notably Brecke,⁹ Fleischner¹⁰ and Ulrici.¹¹

It was therefore thought that a systematic study of such cases with an attempt at topographic localization of the lesion would be of value in clearing up this seemingly controversial question. However, as the material accumulated it became evident that the great majority of lesions presenting the roentgen appearance of the so-called hilus forms

1. Alexander, H.: Ueber Hilustuberkulose bei Erwachsenen, Beitr. z. Klin. d. Tuberk. **62**:318, 1926.

2. Bernard, L.: Le début intercléido-hilaire de la tuberculose pulmonaire, Presse méd. **38**:373 (March 15) 1930.

3. Bernard, L.; Lelong, M., and Renard, G.: La localisation péri-hilaire de la tuberculose pulmonaire chronique de l'adulte, Ann. de méd. **21**:366, 1927; Essai pathogénique sur les localisations de la tuberculose pulmonaire chronique, Ann. de méd. **21**:353, 1927.

4. Faber, K.: Perihilar Pulmonary Tuberculosis in Adults, Hospitalstid. **73**: 879 (Sept. 4) 1930; Perihilar Pulmonary Tuberculosis in Adults, Acta med. Scandinav. **75**:403, 1931.

5. Ghon, A.: Genese und Anatomie der Tuberkulose, in Ghon, A., and Jaksch-Wartenhorst, R.: Die Tuberkulose und ihre Bekaempfung, Vienna, Emil Haim & Co., 1922.

6. Ghon, A., and Kudlich, H.: Zur sogenannten Hilustuberkulose, Med. Klin. **24**:1661 (Oct. 26) 1928.

7. Graeff, S., and Kuepferle, L.: Die Lungenphthise, Berlin, Julius Springer, 1923, vol. 1.

8. Tendeloo, N. P.: Studien über die Entstehung und den Verlauf der Lungenkrankheiten, ed. 2, Munich, J. F. Bergmann, 1931; Pathologische Anatomie, in Brauer, L.; Schröder, E., and Blumenfeld, F.: Handbuch der Tuberkulose, ed. 3, Leipzig, Johann Ambrosius Barth, 1923, vol. 1.

9. Brecke, A.: Allgemeine Diagnostik, in Brauer, L.; Schröder, E., and Blumenfeld, F.: Handbuch der Tuberkulose, ed. 3, Leipzig, Johann Ambrosius Barth, 1923, vol. 1.

10. Fleischner, F.: Lobäre und interlobäre Lungenprozesse, Fortschr. a. d. Geb. d. Röntgenstrahlen **30**:181 and 441, 1923.

11. Ulrici, H.: Zur Frage der sogenannten Hilustuberkulose, Beitr. z. Klin. d. Tuberk. **46**:38, 1921.

were in reality lesions involving the superior portion of the lower lobe, especially its apical and subapical region. This resulted in focusing the attention of this study on the problem of tuberculosis of the lower lobe in general.

Involvement of the lower lobe in pulmonary tuberculosis is generally regarded as an irrelevant and, as a rule, late occurrence in the course of progressive craniocaudate phthisis. Cases in which the lesion starts in the lower lobe are looked on as extreme rarities. It seems that most pathologists and clinicians, as well as roentgenologists, concur in this view. In considering the question whether such statements are in accord with actual conditions, it is necessary to call attention to certain facts which are bound to limit their validity.

With regard to anatomic observations, it must be pointed out that patients with early lesions in which the point of origin can be established with a fair degree of probability rarely come to postmortem examination, while the end-stages of an advanced lesion seldom permit a reconstruction of the topographic and chronological sequence of events. It is probable that a lesion which begins in the lower lobe and subsequently involves the upper lobes may be devoid of any definitely distinguishing features at the autopsy table and may thus present the picture of common progressive craniocaudate phthisis. The great advantage of clinical and roentgenologic follow-up studies in establishing the location of the early lesion and its subsequent evolution is therefore apparent.

With respect to statements from clinical and roentgenologic sources which emphasize the extremely rare occurrence of tuberculosis of the lower lobe, it is important to point out that one frequently fails to make a clear distinction between lesions of the lower lobe and basal lesions, and that these designations are often used promiscuously. This appears to be chiefly due to the fact that the topographic boundaries of the lobes are often lost sight of. Lesions confined to the superior portion of the lower lobe present neither clinical nor roentgenologic features indicative of a basal process and are in many instances responsible for the somewhat vague term hilus tuberculosis.

A sharp differentiation between lesions involving the superior portion of the lower lobe and true basal involvement is of considerable significance. There is no doubt that early involvement limited to the base of the lung is an extremely rare and unusual occurrence in the reinfection forms of adult tuberculosis. This, however, does not apply to the cranial portion of the lower lobe. It is fairly well known that this area is not infrequently the site of secondary changes in relatively early stages of lesions of the upper lobe. This fact was definitely stressed as early as 1888 by Fowler,¹² who pointed out that "the upper

12. Fowler, J. K.: *Localization of the Lesions of Phthisis*. London, J. & A. Churchill, Ltd., 1888.

changes of abortive character or nodular productive disseminations of the type seen in the chronic hematogenous forms,²² which subsequently developed into progressive lesions of the lower lobe. These cases presented thus a transition from the latent and benign type into progressive caseous-cavernous phthisis of the lower lobe. Finally, the mode of secondary involvement of the lower lobe was studied in many cases of lesions of the upper lobe in which the subsequent stages of progression could be observed. It may not be amiss to point out that, owing to the character of the material of our institution in which the advanced forms show a decided predominance, the proportion of cases with early involvement is rather limited. It is probable, therefore, that given a different type of material the number of cases with initial lesions of the lower lobe would be considerably augmented.

INCIDENCE AND CLINICAL FEATURES

In the group of cases with primary involvement of the lower lobe there was found a remarkable predominance of females. In a total of thirty-four cases there were twenty-eight women and only six men. This predominance of the female sex, impressive as it is in itself, becomes particularly striking when the relations to the total number of patients admitted during the same period are considered. Taking as a basis the material from the service of the Metropolitan Hospital, from which the bulk of the instances have been collected and where the incidence could be checked against the total number of patients, the following figures were obtained: Of twenty-seven patients twenty-three were women and only four, men—a ratio of approximately 6:1 in favor of the former. The total number of patients with pulmonary tuberculosis admitted during the same period was 4,494, of whom approximately three-fourths were males and only one-fourth females. According to this calculation, involvement of the lower lobe was observed in the ratio of about eighteen women to one man on the basis of the total material.

A point which deserves attention is the fact that there were four women in this group in whom the pulmonary lesion developed during pregnancy. A further interesting feature is the presence of three cases of silicosis in the small group of six male patients. In these cases the history and findings indicated that the silicosis preceded the tuberculous involvement. Although it cannot be denied that this may be a mere coincidence, considering the very small number of male patients, there is nevertheless a strong possibility that this factor is of some moment. This point, as well as the significance of pregnancy, will be taken up later in the course of the general discussion.

22. Reisner, D.: The Relations Between Extrapulmonary and Pulmonary Tuberculosis, *Am. Rev. Tuberc.* 30:375 (Oct.) 1934.

the lesion is limited to the apex of the lower lobe, the signs may be peculiarly scant or even completely absent and in marked contrast to the roentgen findings. Several authors attempted to explain this discrepancy on the basis that the lesion is centrally located. This, however, is far from correct, as will be shown presently from the roentgen findings. The area which should be examined with particular attention is the interscapular and paravertebral zone, approximately between the fifth and seventh dorsal vertebrae. This location is most likely to yield positive findings in these cases. On the other hand, it is important to point out that certain physical findings obtained in this area are apt to be misleading, and that particular care must be exercised in their evaluation. Because of the vicinity of the vertebral column and of the trachea and large bronchi, alteration of the percussion note and breath sounds is frequently found here in normal subjects.

A further point of interest is a distinct predominance of the right side in lesions of the lower lobe. There were twenty-four patients with lesions on the right side, as against ten in whom the left side was involved. The preference for the right side could be observed to an equal extent in patients with lesions of the upper lobe in whom the lower lobe, especially its apex, became secondarily involved.

ROENTGEN FINDINGS

In analyzing the roentgen findings in tuberculosis of the lower lobe a definite distinction must be made between cases in which there is massive involvement and those in which the lesion is confined to a more or less limited area. In the former the findings are, as a rule, obvious, and the location in the lower lobe can easily be identified as such, while the latter often require painstaking study. Careful fluoroscopic observation, as well as exposures in the oblique and lateral views, are in most instances indispensable for exact determination of the nature and location of the changes.

Of the group of patients presented in this report only a small number showed extensive involvement of the lower lobe. These were patients with more or less acute caseous pneumonic lesions frequently showing rapid progression (fig. 1). Occasionally the lower lobe appears markedly diminished in size. This may occur either in the more chronic cases with cirrhotic contraction or in cases in which the tuberculous process is combined with lobar atelectasis, as is sometimes seen in aspiration following hemoptysis. In such cases the outer margin of the lower lobe can be seen in the sagittal view as a sharp oblique line running from the hilar area outward and downward toward the base. If the lower lobe of the right lung is involved the findings are evident. On the left side the involved lobe may be concealed behind the heart

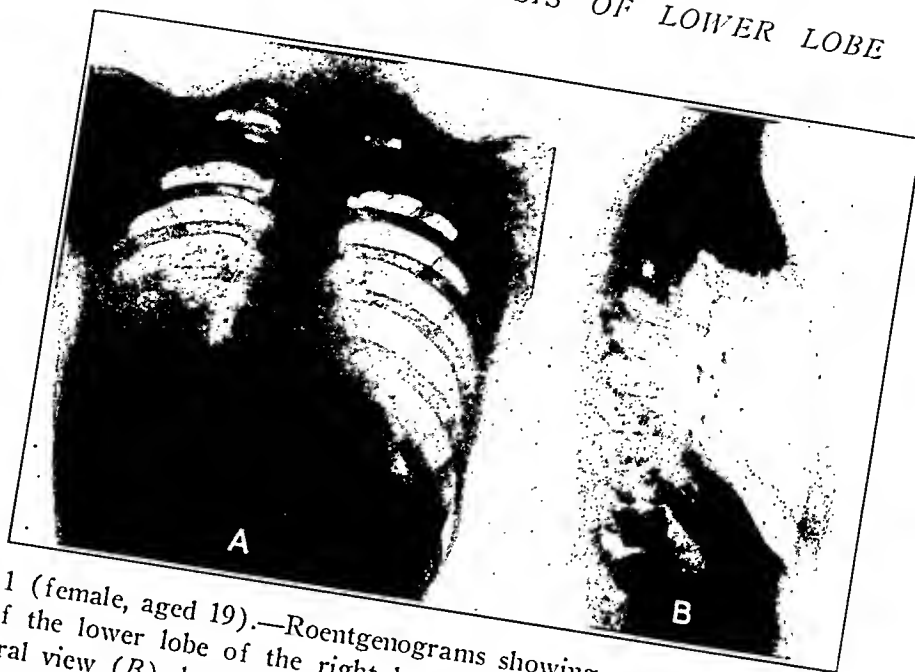


Fig. 1 (female, aged 19).—Roentgenograms showing massive tuberculous pneumonia of the lower lobe of the right lung with probable cavitation at its apex. The lateral view (*B*) demonstrates that the lesion stops abruptly at the interlobar fissure; the heavy density along the margin of the lower lobe is due in part to the superimposed cardiac shadow.

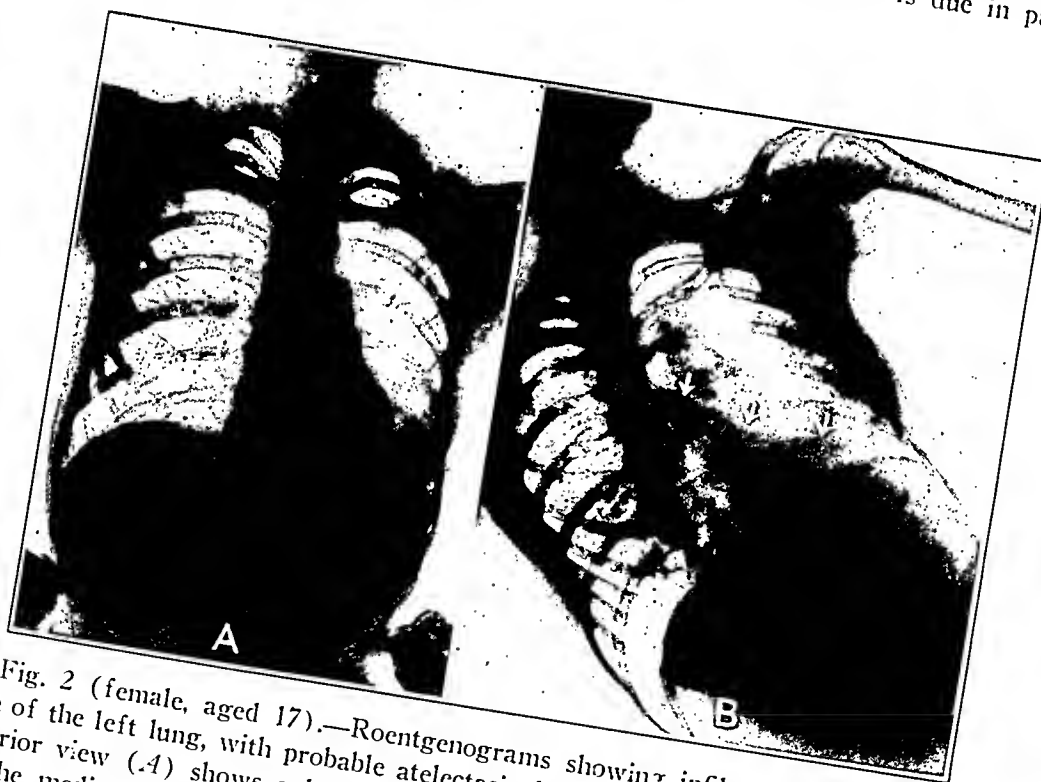


Fig. 2 (female, aged 17).—Roentgenograms showing infiltration of the lower lobe of the left lung, with probable atelectasis following hemoptysis. The postero-anterior view (*A*) shows only indefinite clouding at the base; note the retraction of the mediastinum and heart to the left. The roentgenogram taken with the patient leaning over to the left and in a slightly oblique position (*B*) shows the contracted lower lobe of the left lung as a sharply defined triangular basal shadow with a translucent area in the subapical portion indicating a cavity. These findings were subsequently confirmed after pneumothorax had been established.

shadow, and additional positions have to be employed in order to demonstrate the lesion (fig. 2). Such findings resemble the triangular basal or retrocardiac shadows occasionally observed in chronic non-tuberculous basal lesions.

The predominant majority of patients, however, present involvement of a limited area of the lower lobe, almost invariably of its apical or subapical portion. In practically all the patients of this group there were found cavitations of appreciable size at the time of the first examination; only a very few could be seen in the precavernous stage. This is of considerable interest in view of the brief duration of the symptoms in most cases and indicates that lesions in this location have a decided tendency toward early ulceration and cavity formation. The so-called benign exudative forms which frequently show a great deal of absorption could not be observed in this location.

Changes situated in the apical portion of the lower lobe as a rule appear close to or directly over the area of the root in the roentgenogram taken in the sagittal direction, thus frequently giving the impression of a lesion extending from the hilus. However, further views in other planes reveal that this is merely due to overlapping of densities not related to each other. In the lateral position the infiltration or cavitation is usually seen near the dorsal wall of the chest, not far from the pleural surface projecting over the vertebral column, which indicates that the actual location is in the paravertebral posteromedial zone. Lesions situated at some distance from the apex appear to be farther lateral from the area of the root. In the majority of cases the lesion appears in the sixth or seventh posterior interspace as projected on the wall of the chest. This corresponds with the interscapular area previously mentioned as the most important point where physical signs should be looked for. On the right side the location is frequently somewhat lower than on the left, this evidently being due to the fact that the lower lobe of the right lung is, as a rule, smaller than that of the left. A further important finding is the sharp demarcation of the superior margin of the lower lobe, which can frequently be demonstrated in the oblique or lateral view. This is the case when the process reaches the lobar margin and the adjacent portion of the interlobar pleura (figs. 3 and 4).

The cavities often present the appearance of the thin-walled elastic variety seen in early lesions, or they are surrounded by a zone of exudative infiltration. Because of the apparent proximity to the root their identification is not infrequently difficult. The markings radiating from the hilus and the fact that the boundaries of the annular shadow are partly concealed behind the structures of the root may often be confusing in attempting their exact identification. On the left side the

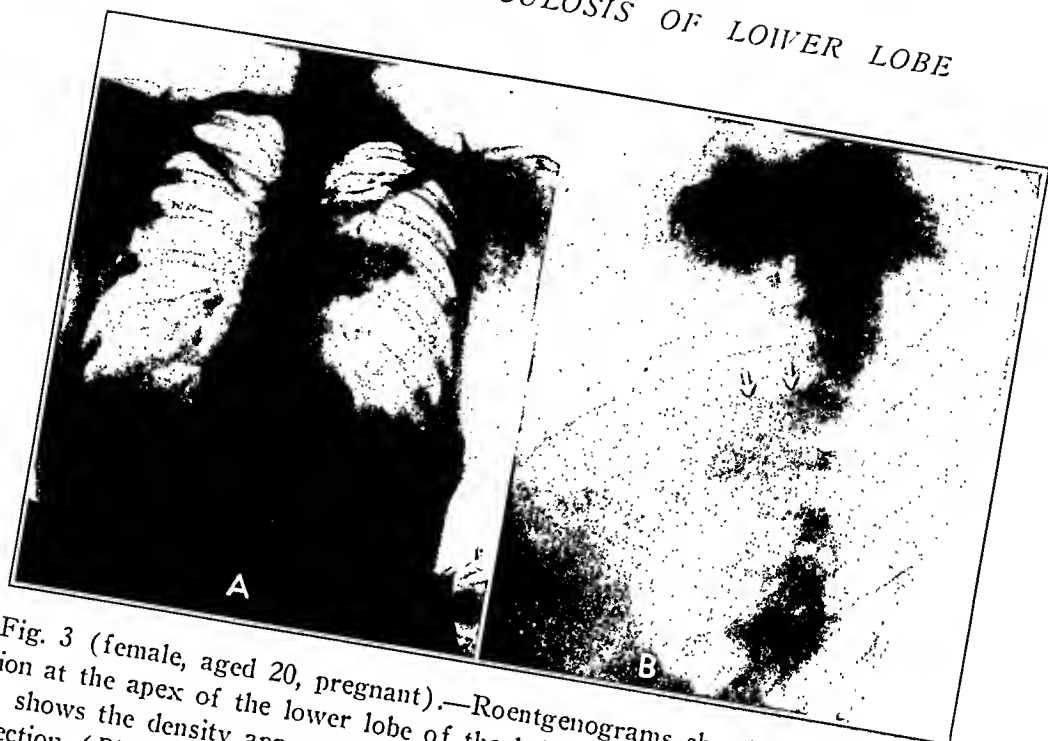


Fig. 3 (female, aged 20, pregnant).—Roentgenograms showing exudative infiltration at the apex of the lower lobe of the left lung. The postero-anterior view (A) shows the density apparently extending from the hilus. The postero-oblique projection (B) demonstrates the location in the apex of the lower lobe, with a sharp demarcation of the lobar margin.

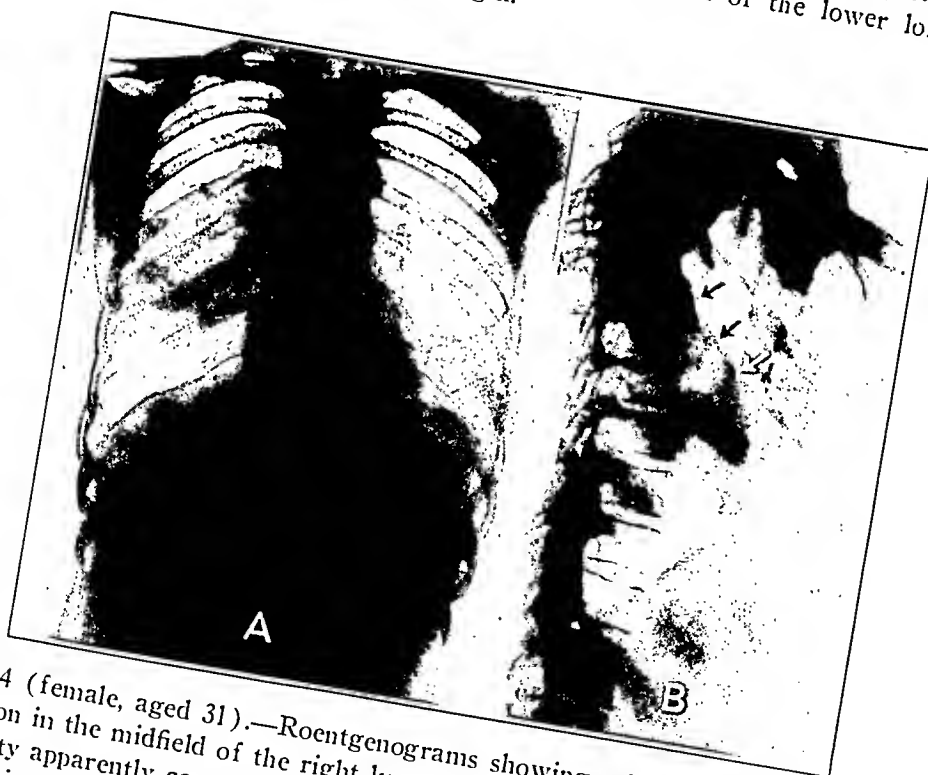


Fig. 4 (female, aged 31).—Roentgenograms showing a large area of pneumonic infiltration in the midfield of the right lung. The postero-anterior view (A) shows the density apparently connected with the area of the root and the cavity projecting into the sixth posterior interspace. The lateral view (B) demonstrates the lesion in the superior portion of the lower lobe, with a sharp demarcation of its margin and the cavity over the sixth dorsal vertebra. There is a deformity of the upper part of the dorsal spine due to old tuberculous caries.

cavity may easily be concealed behind the shadow of the heart. Fluoroscopic studies and additional views, as has already been mentioned, frequently prove of great value (figs. 5, 6 and 7). The demonstration of a fluid level is extremely helpful in these cases. It is of interest that retention of fluid was far more frequently observed in cavities of the lower lobe than in those of the upper lobe. The collection of fluid may be large, and the cavity may thus resemble a nontuberculous abscess

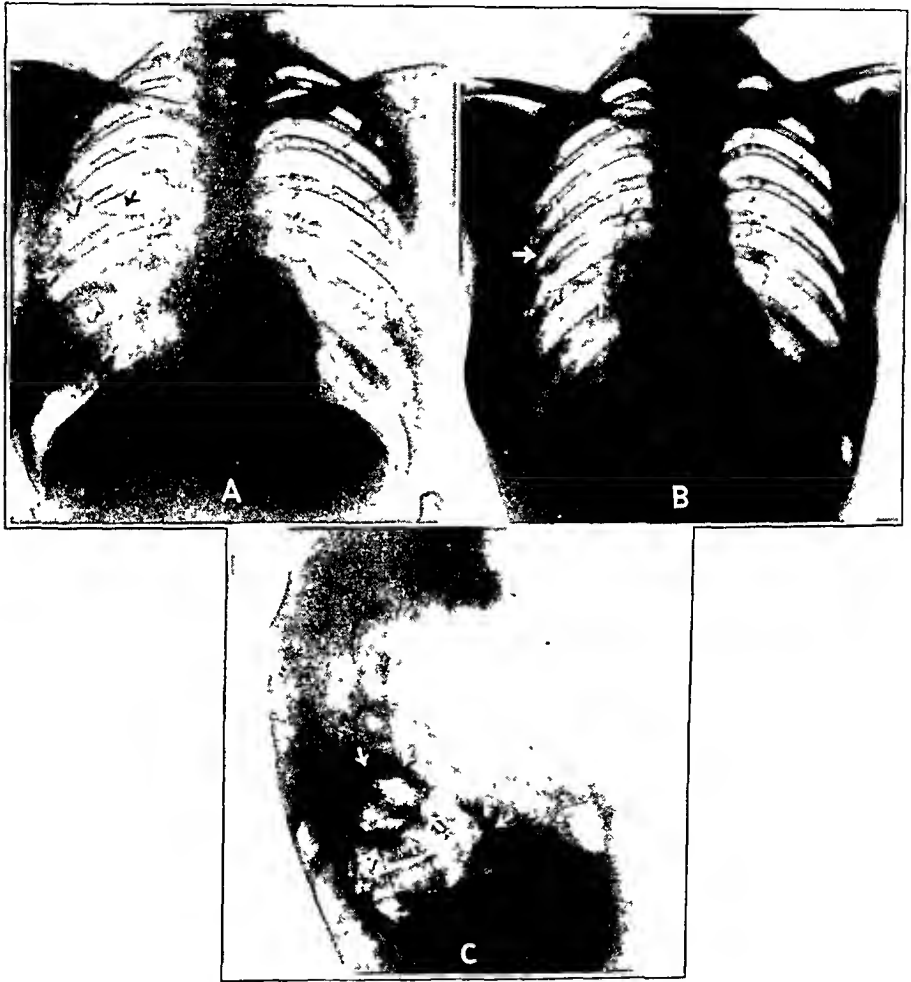


Fig. 5 (female, aged 26).—The postero-anterior view (*A*) shows a large cavity in the midfield of the right lung close to the hilus, with focal infiltration down to the base. The antero-posterior exposure (*B*) demonstrates the cavity more clearly defined and smaller, indicating its posterior location. The lateral view (*C*) shows the cavity close to the posterior wall of the chest, over the spinal column, located in the apex of the lower lobe; there is infiltration along the lobar margin down to the diaphragm.

(fig. 8). The reason for this is evidently the fact that the anatomic position of the bronchi renders conditions of drainage less favorable in this location than in cavities situated in the upper lobe.

extend directly from the apex of the lower lobe into the adjoining area of the upper lobe. The preference for the apical region holds true to an equal extent for secondary changes of the lower lobe which occur in the course of a progressive lesion of the upper lobe.

In the group of cases of primary tuberculosis of the lower lobe there were only a few instances in which the lesion remained limited

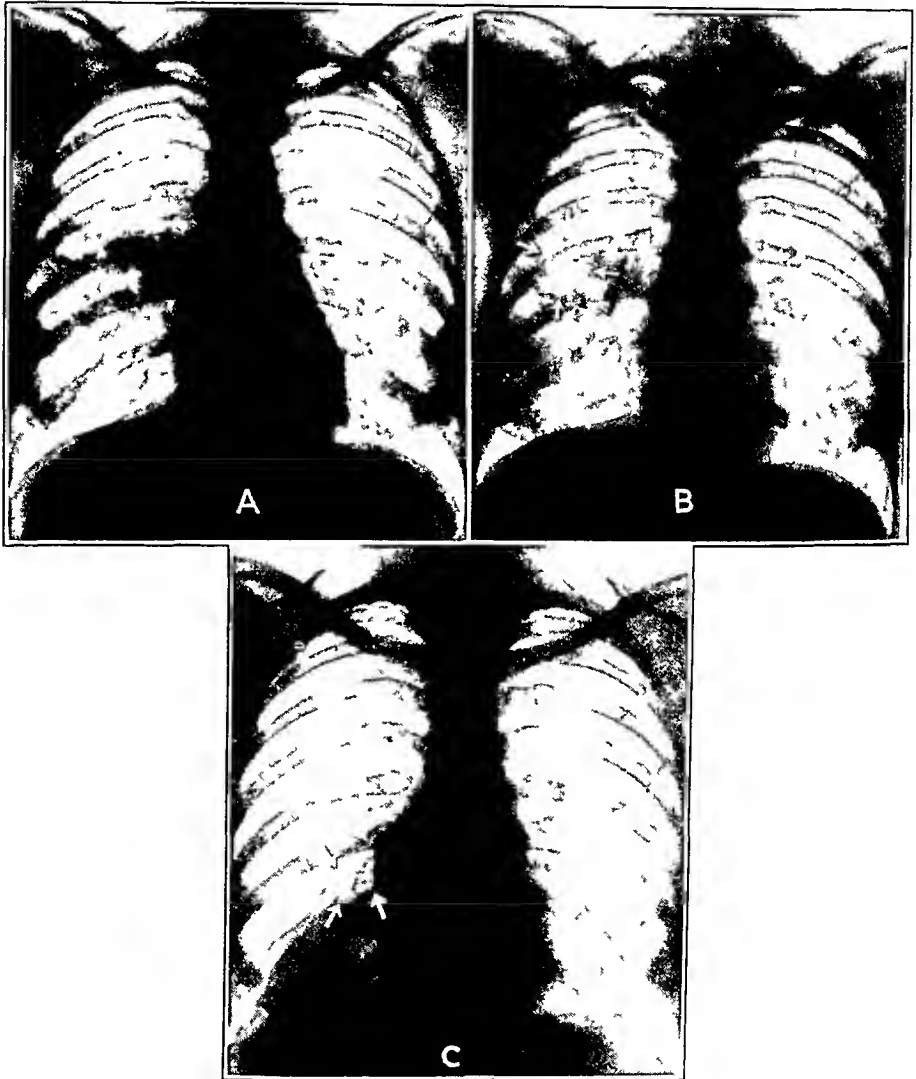


Fig. 7 (female, aged 19) — *A* shows exudative infiltration in the midfield of the right lung, apparently extending from the hilus. Three months later (*B*) there was a distinct cavity, with focal spread to the base. After pneumothorax had been instituted (*C*) there was selective collapse of the lower lobe; the cavity is distinctly seen at its apex.

to the originally involved area for any length of time. In most cases there occurred a bronchogenous spread into other portions of the lung. A fairly characteristic and frequently encountered mode of spread is a

and near their margins, in the middle lobe of the right lung or in the lingula of the upper lobe of the left lung. These locations, however, represent, as a rule, secondary manifestations of progressive bronchogenous tuberculosis. The possibility of localized interlobar or paramediastinal pleurisy may also have to be considered. In such instances further study in various positions demonstrates the respective lobar relations of the lesion in question.

In the vast majority of cases a thorough roentgen examination will reveal the nature of the changes giving the appearance of the so-called hilus lesions. It will demonstrate that such findings in reality represent merely parenchymal changes which happen to be situated in certain regions of the lung, but are otherwise not characteristic or essentially different from corresponding forms of tuberculous changes elsewhere

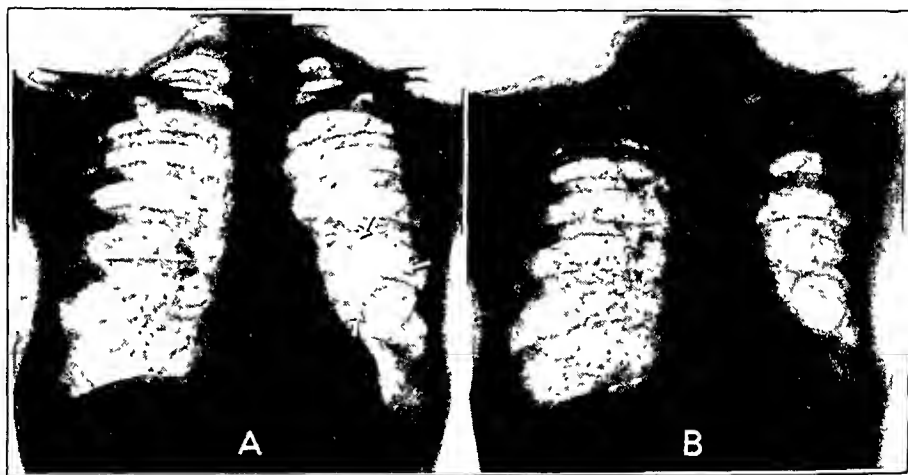


Fig. 9 (female, aged 32).—*A* shows a large cavity in the region of the left hilus (arrows), located in the superior portion of lower lobe, and a smaller cavity farther down and lateral. There were a few soft foci in the upper lobe of the right lung and scattered old calcified nodules in both lungs. Three years later (*B*) there were extensive infiltration and cavitation of the upper lobe of both lungs; the lower lobe of the left lung appeared contracted, and the cavity was surrounded by a dense wall.

in the lung. Of course, the possibility of enlarged tracheobronchial lymph nodes as the basis for the roentgen findings will have to be excluded. It seems fair to state, therefore, that, so far as adult tuberculosis is concerned, there are very few instances in which the findings obtained after an exhaustive roentgen analysis still justify the assumption of some anatomic or pathogenetic relationship with the hilar structures. This is entirely in agreement with the opinion expressed by Fleischner¹⁰ and substantiated by postmortem observations, as was mentioned at the outset of this paper.

It appears, therefore, that, with the possible exception of actual basal locations, artificial pneumothorax is the procedure of choice in lesions of the lower lobe as well as in those of the upper lobe. If pneumothorax is not feasible or if the results are unsatisfactory more radical measures of surgical collapse should be employed.

COMMENT

In discussing the problem of tuberculosis of the lower lobe the question arises whether such locations represent nothing further than occasional atypical occurrences which are merely exceptions to the general rule. That this is evidently not the case is indicated by the almost invariable location of the early changes in a distinct portion of the lower lobe, that is, in its apical or subapical area, and furthermore by the curious predominance of these lesions in women. These facts are so striking that they call for an explanation.

It is an indisputable fact as well as a matter of common knowledge that there are certain regions of the lung which are more prone to tuberculous involvement than others. It is likewise well established that the primary focus in childhood shows a decidedly different location in the lung than the early manifestations due to reinfection or superinfection in adult life. To be sure, the question as to what constitutes these differences in susceptibility has not been answered to complete satisfaction as yet. It lies beyond the scope of this paper to enter into a full discussion of the theories which have been advanced on this subject. It is probable, however, that the responsible factors are intimately related to the anatomic configuration of the adult thorax, as contrasted with the type seen in children; furthermore, that the physiologic mechanism of respiration is of considerable influence. It seems most plausible that the restricted ventilation and consequent impairment of the circulation of the blood and lymph in certain parts of the lung create particularly vulnerable areas.

Of more immediate concern, however, in connection with the subject of this paper is the question of the topographic definition of the predisposed region of the lung. To begin with, it is important to point out that the significance attached to the apex as a site of initial manifestations of progressive forms of the adult type of tuberculosis has unquestionably been overemphasized in the past. In view of the present knowledge, it would seem far more correct to use the broader term cranial zone instead. What are the anatomic boundaries of this zone? According to Tendeloo,^s the area of predisposition comprises the cranial fourth of the lung. This author states that there is a minimum of variation in respiratory volume in this region, especially in the posterior

the summit. The degree of diaphragmatic respiration is thus in an inverse ratio to the distance from the base. This may have a bearing on the fact that the location of early lesions diminishes in frequency from above downward.

The location of the upper limit of the area expanded by the diaphragm depends probably to a great extent on individual variations. Tendeloo⁸ placed this limit at the level of the fifth rib, which is evidently intended to indicate an average. There is no doubt, however, that there are variations in the upward or downward direction according to the extent of diaphragmatic movements. The apex of the lower lobe represents thus a borderline zone, and it depends largely on the effectiveness of the diaphragmatic function whether or not this region is included within the range of the area of lessened resistance.

It seems probable that this mechanism has an important bearing on the question of involvement of the lower lobe in tuberculosis and, more specifically, on the striking finding that this occurs predominantly in females. The difference in the type of respiration in men and women seems to offer a plausible explanation. It is a matter of common knowledge that in men the lung is expanded chiefly by the diaphragmatic movements, whereas in women the costal type of breathing is the predominant factor. A lucid description of these respiratory types was given by Hutchinson²⁸ as early as 1846 and more recently by other writers, especially de la Camp²⁹ and Keith.²⁷ The variations in the behavior of the diaphragm are most convincingly demonstrated on fluoroscopic observation.

In view of the more limited diaphragmatic excursions in women, it is only logical to assume that the superior boundary of the pulmonary area ventilated by the diaphragm is, on an average, at a lower level in women than in men. It is, therefore, reasonable to expect that the zone of predisposition comprises a larger area in the former and that it extends farther down, including a portion of the lower lobe, chiefly its apical region.

Thus, with all other factors remaining equal (as an equal infective dose and an equal state of immunity), there seems to be a considerably greater chance for involvement of the lower lobe in women than in men. It goes without saying, of course, that in the vast majority of cases the early changes are found in the upper lobe in women as well. However, while in men the lower lobe is, as a rule, better equipped to withstand the injurious effect, in women its superior portion seems to

28. Hutchinson, J.: On the Capacity of the Lungs and on the Respiratory Function, *Med.-Chir. Tr.*, London **29**:137, 1846.

29. de la Camp: Beiträge zur Physiologie und Pathologie der Zwerchfellathmung, einschliesslich der zugehörigen Herzbewegungen, *Ztschr. f. klin. Med.* **49**: 411, 1903.

There are undoubtedly other factors than those directly related to the respiratory mechanism that may promote the development of a tuberculous lesion in unusual locations. The possibility that such factors may be present should be especially considered when these lesions are found in male patients. The cases of silicosis observed in this series offer an interesting example in this connection. It seems likely that the block of lymph vessels and the impairment of lymphatic drainage which take place in this condition affect the defense mechanism of the lung and cause a complete alteration in the range of susceptibility of its various regions. Subsequent tuberculous infection may thus lead to atypically located lesions in such cases. Gardner³⁴ recently called attention to the fact that tuberculous changes complicating silicosis frequently occur in atypical areas, especially in the middle or lower pulmonary field. The occurrence of atypical forms and locations of pulmonary tuberculosis in diabetes is an example of a different nature. It is possible that a change in tissue reactivity resulting from the metabolic disorder may be of significance in furthering such developments. Tuberculous lesions in uncommon locations are also not infrequently met with in persons of advanced age and in patients with kyphosis or kyphoscoliosis (von Hanseemann,³⁵ Ranke,³⁶ Loeschcke²⁶). In these conditions, however, the responsible factors are probably related to the altered configuration of the thorax and its effect on the respiratory mechanism, as was particularly emphasized by Loeschcke.

Finally, it must be mentioned that there occur various transitional respiratory types in both sexes, depending on the general constitutional habitus, such as a predominantly diaphragmatic type of breathing in women or a chiefly costal type in men. The latter fact may be of some consequence with respect to the sporadic occurrence of lesions of the lower lobe in males. However, it seems reasonable that the chances for development of tuberculosis of the lower lobe are far greater in women, as they are under a distinct potential disadvantage which is evidently determined by physiologic limitations.

In conclusion, a few remarks should be made regarding the clinical differential diagnosis of tuberculosis of the lower lobe. It has been variously stated that lesions of the lower lobe must be considered non-tuberculous unless proved otherwise. This is probably true, so far as strictly basal locations are concerned. In such cases definite clinical or roentgenographic features indicative of tuberculosis may be absent,

34. Gardner, L. U.: Inhaled Silica and Its Effect on Normal and Tuberculous Lungs, *J. A. M. A.* **103**:743 (Sept. 8) 1934.

35. von Hanseemann, D.: Ueber typische und atypische Lungenphthise, *Berl. klin. Wchnschr.* **48**:1 (Jan. 2) 1911.

36. Ranke, K. E.: Die Tuberkulose der verschiedenen Lebensalter, *München. med. Wchnschr.* **60**:2153 (Sept. 30) 1913.

artificial pneumothorax is the procedure of choice, despite the location in the lower lobe.

The roentgen findings in tuberculosis of the lower lobe are discussed, and it is emphasized that changes in its apical region frequently present the misleading appearance of so-called hilus lesions. It is also stressed that in general there is no adequate foundation for the conception of a hilar form of pulmonary tuberculosis as a pathogenic entity.

Tuberculosis of the lower lobe occurs principally in women and is very uncommon in men. An explanation of this difference in the behavior of the sexes has been attempted on the basis of existing physiologic variations in the respiratory mechanism.

2 East Eighty-Fifth Street.

The pulse was thready and at times imperceptible, its rate being about 40. A cursory examination revealed an incised wound about 4 cm. to the left of the mid-sternal line at the level of the sixth rib. The symptoms of obstruction to the venous inflow of the heart, probably the result of rapidly developing hemopericardium, led to a diagnosis of cardiac tamponade, and the patient was hurried to the operating room. On his arrival there, about five minutes after admission, the radial pulse and heart sounds were imperceptible; respiratory movements were absent, and the pupils were dilated and fixed. Indeed, the only signs of life were questionable quivers of the lower lid and of the upper abdominal muscles. It was decided that any delay in treatment, no matter how short, would make death certain. Operation was therefore begun without undressing or moving the patient from the cart, without attempting sterilization of the skin or hands of the operators and with a limited number of instruments. During the course of the operation sterile instruments and dressings were obtained.

The pericardial sac was exposed by a curved incision to the left of the sternum through three costal cartilages with removal of a segment of the sixth costal cartilage. The pericardial sac was markedly distended, and an incised wound was noted on its anterior surface. The wound was enlarged, and about 250 cc. of clotted and liquid blood was evacuated. The absence of bleeding, anesthesia, respiratory movements and sterile surroundings up to this point were more suggestive of an autopsy than an operation. When exposed the heart was observed to be in a state of standstill or prolonged diastole. After it was grasped, a few beats occurred at intervals of two or three seconds. The rate quickly increased to about 120 with a regular rhythm and remained unchanged during the remainder of the operation. Respirations were resumed immediately on evacuation of the pericardial sac. An incised wound about 3 cm. long was observed in the middle third of the anterior wall of the right ventricle 1.5 cm. to the right of, and parallel to, the descending branch of the left coronary artery. In an attempt to control the bleeding from this wound two fingers were inadvertently pushed into the chamber of the right ventricle. The wound was closed with four interrupted catgut stitches, the adjacent coronary artery being avoided. The pericardium was closed tight. The wall of the chest was sutured, and a Penrose drain was inserted to, but not into, the pericardium. At no stage was anesthesia necessary. During the latter part of the operation 500 cc. of physiologic solution of sodium chloride and a solution of 10 per cent dextrose, followed by 500 cc. of citrated blood, were given intravenously. Semiconsciousness returned during the transfusion. The blood pressure, now obtainable for the first time, was 78 systolic and 48 diastolic. The patient was undressed and put to bed. The respiratory rate was 48; the pulse rate, 92, and the axillary temperature, 99 F. One hour later the blood pressure was 100 systolic and 64 diastolic. During the night the patient recovered consciousness and became so restless that morphine had to be administered.

During the next two days his general condition remained only fair, and he was delirious most of the time. Roentgen examination revealed moderate enlargement of the cardiac shadow and a small amount of air in the upper part of the left pleural space. Transfusion of 300 cc. of citrated blood was followed by a moderately severe reaction. About sixty-eight hours after operation the patient's condition suddenly became much worse. The pulse was barely perceptible; the skin became cold and clammy, and nausea and vomiting were severe. Aspiration of 175 cc. of bloody fluid from the pericardial sac resulted in rapid relief from the symptoms of cardiac tamponade. Twelve hours later the syndrome recurred, and aspiration was again required. The fluid now obtained was turbid and contained numerous staphylococci; so the pericardial sac was widely opened. Within twenty-

four hours the exudate from the pericardial sac had become frankly purulent. During this period pulsus paradoxus and at times pulsus alternans were noted. During the next six days the temperature fluctuated between 98 and 103 F., and the pulse rate, between 88 and 110. The patient was delirious at times and urinated involuntarily. The discharge from the pericardium became thick and purulent. The contractions of the heart churned the fibrinous exudate in the pericardial sac into masses as large as 2 cm. in diameter, which interfered with free drainage from the sac. For this reason irrigations of the pericardial sac with surgical solution of chlorinated soda every two hours while the patient was awake were begun on the tenth postoperative day and were continued with diminishing frequency for eighteen days. These irrigations often produced abdominal and pre-

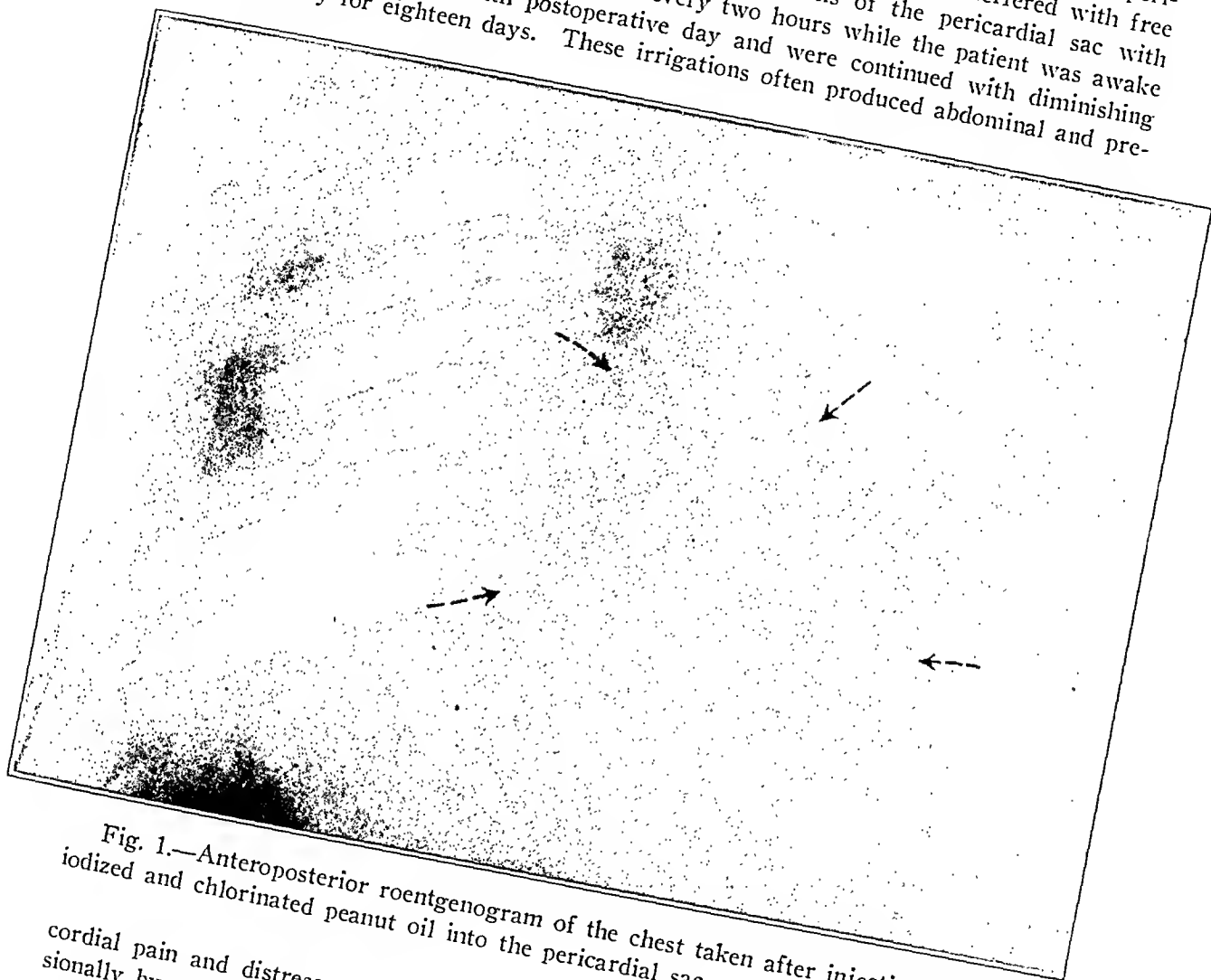


Fig. 1.—Anteroposterior roentgenogram of the chest taken after injection of an iodized and chlorinated peanut oil into the pericardial sac.

cordial pain and distress and were followed within an hour by nausea and occasionally by vomiting.

By the twenty-eighth postoperative day the discharge from the pericardial sac had diminished in amount, and physiologic solution of sodium chloride was substituted for the surgical solution of chlorinated soda in irrigating the sac. At this time curiosity as to the degree of obliteration of the sac prompted us to investigate the matter by injecting an iodized and chlorinated peanut oil into the sac and examining the chest roentgenologically (figs. 1 and 2). The oil was found collected in small pools and distributed unevenly in the sac. None could be seen on the posterior or left wall; it appeared to be confined to an oval area about 7 by 10 cm. at the side of the anterior or right wall of the pericardial sac, and some was collected in the pool at the base of the heart.

On the thirtieth postoperative day, just two days after discontinuation of the irrigations with surgical solution of chlorinated soda, ascites was noted, and the liver was found to be enlarged and tender. An encapsulated hydrothorax appeared at this time, first on the right side and then on the left, of sufficient volume to cause distressing dyspnea. The pleural fluid was aspirated and found to be clear and sterile.



Fig. 2.—Lateral view of the chest taken after injection of an iodized and chlorinated peanut oil into the pericardial sac.

By the end of the fifth postoperative week the temperature rose daily to approximately 100 F., and the pulse rate fluctuated between 100 and 108. The pericardial opening had contracted to about 2 cm. in diameter, and the discharge was seropurulent and small in amount. However, the evidences of circulatory embarrassment became progressively more marked; by the seventh week the abdomen was tense, and edema of the subcutaneous tissues, especially those of the face and chest, was marked. The pulse rate had increased to between 110 and 150, and the volume of the pulse was small. The temperature had risen so that a

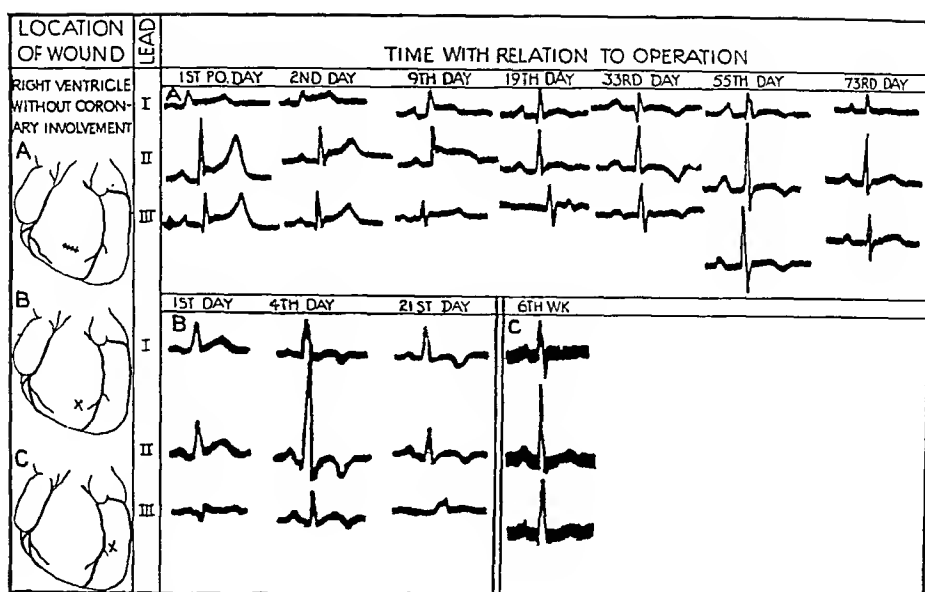


Fig. 3.—Diagrams showing position of the wound and electrocardiograms obtained (A) in case 2 of Porter and Bigger (tracings taken from Porter and Bigger¹⁰); (B) in the case of Schlomka (tracings taken from Schlomka⁸), and (C), in the case of Cole (tracings taken from Cole⁴).

In this figure and in the following figures, the line with cross-hatching indicates injuries exactly located by the author; X, those located only approximately.

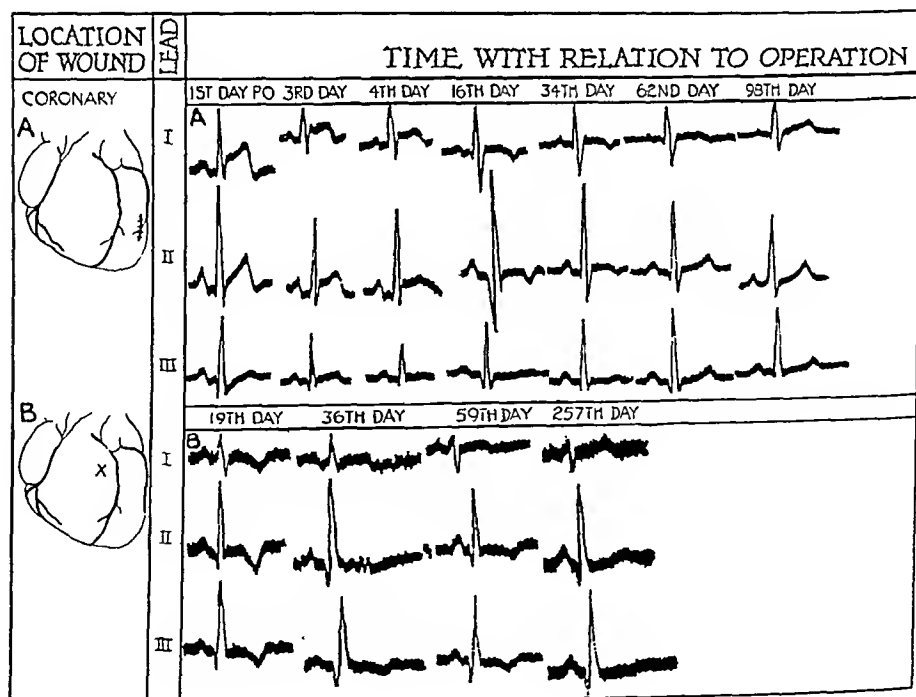


Fig. 4.—Diagrams showing location of the wound and electrocardiograms obtained (A) in case 1 of Porter and Bigger (tracings taken from Porter and Bigger¹⁰) and (B) in the case of Davenport (tracings taken from Davenport⁵).

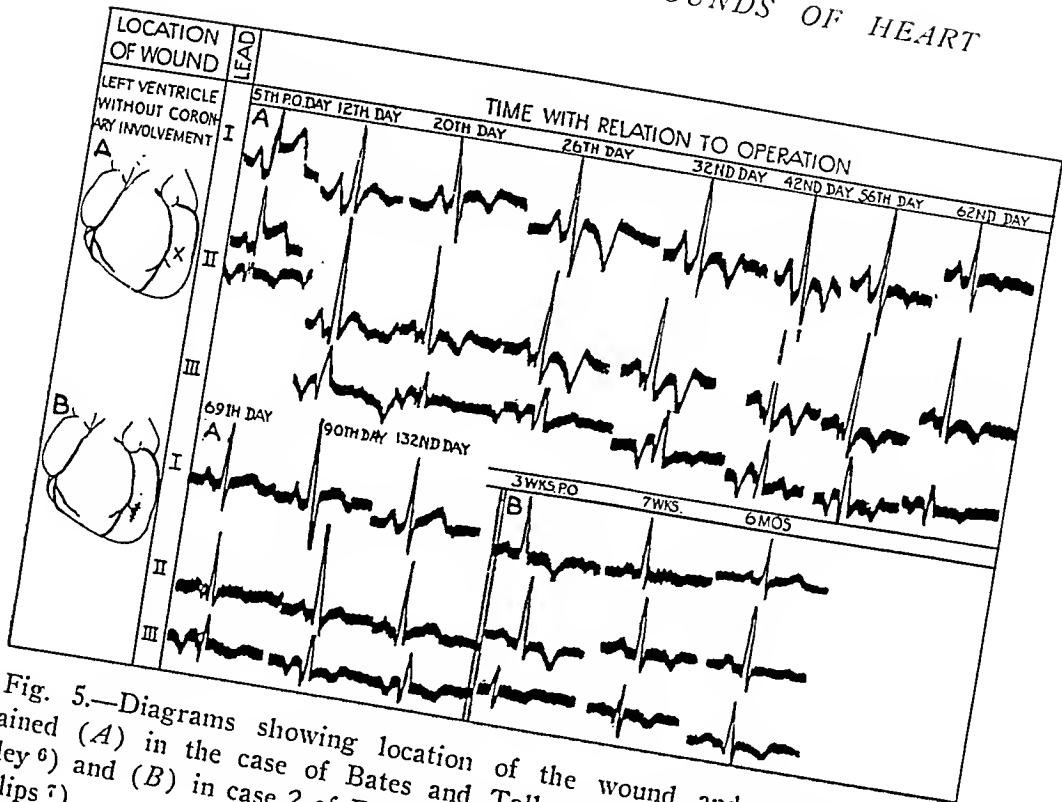


Fig. 5.—Diagrams showing location of the wound and electrocardiograms obtained (A) in the case of Bates and Talley (tracing taken from Bates and Talley⁶) and (B) in case 2 of Elkin and Phillips (tracings taken from Elkin and Phillips⁷).

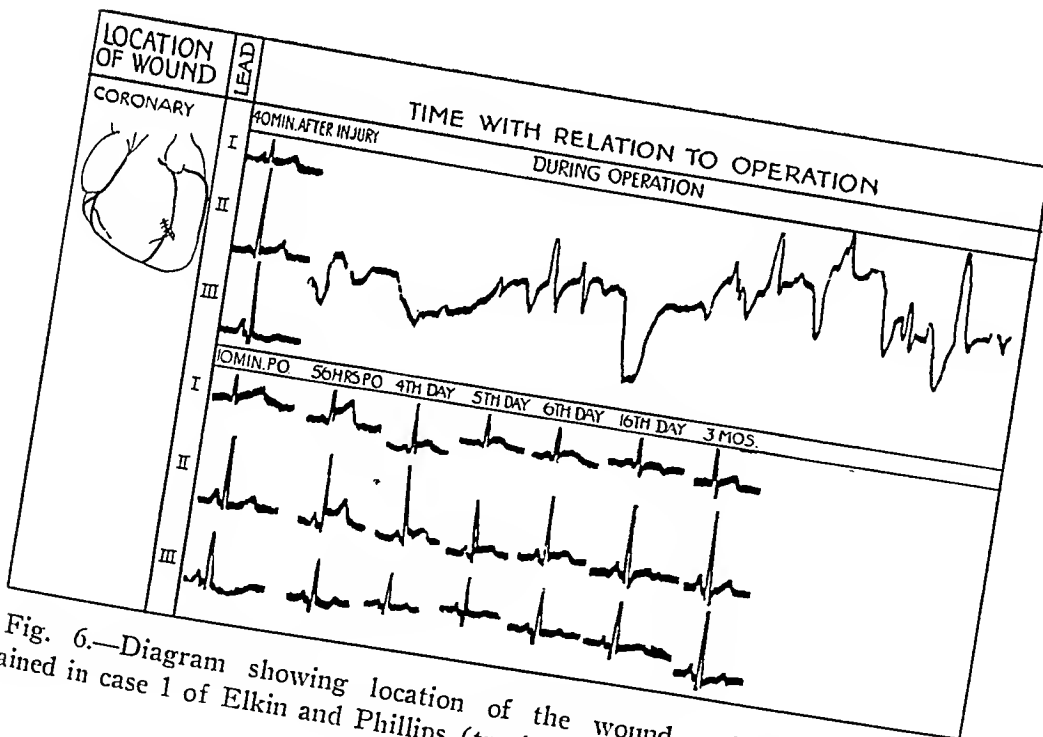


Fig. 6.—Diagram showing location of the wound and electrocardiograms obtained in case 1 of Elkin and Phillips (tracing taken from Elkin and Phillips⁷).

Elkin and Phillips⁷ reported two cases in which electrocardiograms were obtained. In the first case the anterior descending branch of the left coronary artery was divided and had to be ligated. Recovery was complete (fig. 6). The first electrocardiogram was made forty minutes after the injury and immediately after operation. It was essentially normal. A tracing made during the operation gave a bizarre QRS complex and nondescript curves. Another tracing made ten minutes after the operation disclosed a slightly elevated take-off in lead I and a depressed take-off in lead III. Fifty-six hours later leads I and II were characterized by a high take-off which, while still elevated, became lower by the fourth postoperative day and disappeared, to be replaced on the sixteenth day by an inverted T wave. Three months after operation the tracings had become normal.

In the second case the stab wound was in the right ventricle and, at the most, involved only a small branch of the descending branch of the left coronary artery (fig. 5 B). The first tracing made three weeks postoperatively disclosed an inverted T wave in all the leads. Seven weeks after the operation the T wave was diphasic and in leads II and III was inverted. Six months after operation the only remaining change was an inverted T wave in lead III.

Schlomka⁸ reported a case of stab wound on the anterior aspect of the right ventricle without apparent involvement of the coronary arteries (fig. 3 B). The electrocardiogram on the first day showed a slight elevation of the take-off, which was replaced on the fourth day by an inversion of the T wave in all leads. This inversion was still present in leads I and II on the twenty-first day. Lead III was of low potential throughout.

Purks⁹ included an interesting report of an 18 year old colored youth, who was operated on fifty minutes after being stabbed. The wound had penetrated the right ventricle parallel to the anterior descending branch of the left coronary artery. The artery was cut and had to be ligated. Electrocardiograms (fig. 7) were taken before, during and after operation. The curve obtained before operation displayed a slightly elevated take-off in leads I and II. Tracings made during operation showed bizarre QRS complexes and nondescript curves. Ten minutes after operation the take-off for the T wave in lead I was definitely elevated while that in lead III was depressed. These changes persisted in the tracings with only a gradual diminution in degree until, and including, the one made on the sixth day. On the twelfth day the T wave was diphasic in leads I and II and was inverted in lead III. On

7. Elkin, D. C., and Phillips, H. S.: *J. Thoracic Surg.* **1**:113, 1931.

8. Schlomka, G.: *Deutsche med. Wchnschr.* **57**:630, 1931.

9. Purks, W. K.: *Am. Heart J.* **7**:101, 1931.

time in either case. The authors in discussing this point explained the absence of pain on the basis of the loss of muscular contractions due to the severance of the muscle fibers, and they emphasized the factor of muscular work in the explanation of pain from occlusion of the coronary arteries. In support of this theory they referred to the case of Burian,¹¹ in which a branch of the coronary artery was divided with only superficial injury to the muscle. The vessel was ligated. Postoperatively, anginal pain was a troublesome symptom.

Schmidt-Weyland¹² reported a case of attempted suicide occurring in 1895 in which the heart was wounded by a bullet from a pistol. Surgical repair was made. In 1907 the patient complained of an occasional sense of pressure and stabbing pain in the region of the heart. The lips were slightly cyanotic; the pulse rate at that time was 48. In 1930 the patient had no cyanosis. The heart was of normal size; the blood pressure was 170 systolic and 70 diastolic. The patient had a total heart block, and the electrocardiograms, which were not reproduced in the report, were described as follows: T wave diphasic in leads I and II; P wave diphasic in all leads.

Baledent and Bizard¹³ reported a case in which extrasystoles occurred at long intervals after a stab wound of the heart immediately below the auriculoventricular ring in the left ventricle. The electrocardiograms showed a right ventricular extrasystole in leads I and II, which the authors regarded as possibly septal in origin.

Ramsdell¹⁴ reported a case of symptomatic recovery but with a persistently inverted T wave after five months.

ELECTROCARDIOGRAPHIC FINDINGS IN OUR CASE

Electrocardiograms in our case (fig. 8) disclosed a high take-off of the T wave (Pardee curve) in both the first and the second lead with low voltage in all leads on the day after operation. By the fifth day the take-off was still elevated, although not as high as before, and lead III, which on the first day was almost iso-electric, displayed a higher voltage with an inverted T wave.

On the ninth day the high take-off was still present in the first and second leads; the T wave was upright in the third lead; on the fifteenth day the take-off was only slightly elevated with the convexity upward to an inverted T in leads I and II, and the T wave in lead III was iso-electric.

11. Burian, F.: *Casop. lék. česk.* **61**:585, 1922.

12. Schmidt-Weyland, P.: *Deutsche med. Wchnschr.* **57**:2014, 1931.

13. Baledent, M., and Bizard, G.: *Compt. rend. Soc. de biol.* **103**:730, 1930.

14. Ramsdell, E. G.: *Ann. Surg.* **49**:141, 1934.

On the twenty-fifth day a well marked inversion of the T wave was present in all three leads and still persisted on the forty-fourth day.

Five months after operation the electrocardiogram was entirely normal in all three leads.

The electrocardiograms in the cases already cited were copied and arranged according to the site of injury (figs. 3 to 8). The electrocardiographic tracings obtained showed no relation either to the location of the injury or to ligation of the coronary arteries. We must add, however, that in each case the wound was on the anterior surface of either the right or the left ventricle. In Purk's case an electrocardiogram obtained before operation disclosed a slight elevation of the take-off for the T wave in leads I and II, while the electrocardiogram made before operation in case 1 reported by Elkin and Phillips⁷ showed practically no change from the normal tracing. Both these authors obtained

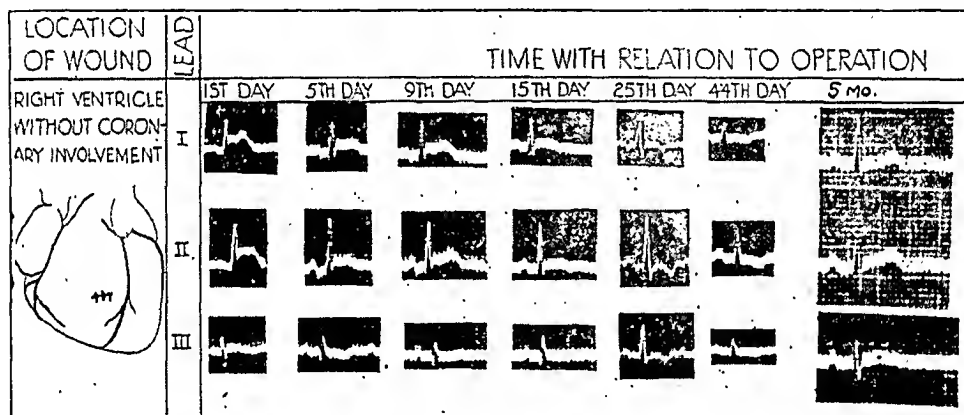


Fig. 8.—Diagram showing location of the wound and electrocardiograms taken in our case.

a tracing during operation showing irregular and bizarre QRS waves. Tracings made a few minutes postoperatively in these cases disclosed an elevated take-off for the T wave in lead I and a concave take-off to an inverted T wave in lead III. A high take-off developed and persisted until from the fourth to the sixth day in all of the cases reported, except in case 2 of Porter and Bigger, in which it persisted until the ninth day, and in Schlomka's case, in which it had disappeared from the tracing on the fourth day. Since in most of the tracings an interval of from six to ten days occurred between the last tracing showing a Pardee curve and the first one in which it was absent, one may assume that it persists for from about four to ten days postoperatively. It is uniformly replaced by an inverted T wave which in some instances (Purk's case on the sixteenth day) goes through a diphasic stage. This stage persists for a variable period of from about four to twelve weeks. A low potential (Porter and Bigger [case 2] and Davenport) and a

notched R wave in lead III (Bates and Talley) occurred but were not constant. A return to a normal curve apparently occurs ultimately in the vast majority of cases.

POLYSEROSITIS (PICK'S SYNDROME)

The development and sudden disappearance of the anasarca in this case merits further consideration. Pool¹⁵ discussed the treatment of purulent pericarditis and reported the occurrence of abdominal distention and generalized edema after irrigation of the pericardial sac with surgical solution of chlorinated soda for ten days. The irrigations were discontinued because the amount of discharge had become small. The generalized anasarca disappeared in two weeks. Other authors cited by Pool reported no ill effects from the same procedure.

Beck^{3a} injected surgical solution of chlorinated soda into the normal pericardial sac of dogs and found that it caused pain and bleeding. The pulse rate usually increased promptly after the solution was introduced. Within a few weeks pericarditis, with either effusion or adhesions, resulted. Generalized edema and polyserositis occurred in a few instances.

Subsequently, Beck and Griswold^{3b} reported results obtained in a larger series of dogs. Surgical solution of chlorinated soda was injected into the pericardial sac, and a rise in venous pressure, polyserositis and, finally, edema resulted in some of the animals. The authors concluded that Pick's syndrome is due essentially to the inability of the heart to fill because of the diminished capacity of the pericardial sac. Pericardiectomy when instituted sufficiently early resulted in recovery, an observation partially verified in one patient.

Cox¹⁶ reported two cases of wounds of the heart. In the second case generalized anasarca and dyspnea developed rather acutely on about the thirty-seventh postoperative day. Forty-six days later, after treatment with digitalis and merbaphen, the patient recovered. One year later there was no evidence of cardiac insufficiency.

PERICARDITIS AND POLYSEROSITIS IN OUR CASE

Pericarditis developed in our case, and the pericardial sac was opened widely. Irrigations with surgical solution of chlorinated soda were begun and continued at decreasing intervals for eighteen days. Many of the irrigations were accompanied by thoracic and abdominal pain and were followed within an hour by nausea and occasionally by vomiting. On the twenty-eighth postoperative day an iodized and chlorinated peanut oil was injected into the pericardial sac, and roentgenograms were

15. Pool, E. H.: *Ann. Surg.* **73**:393, 1921.

16. Cox, D. M.: Wounds of the Heart, *Arch. Surg.* **17**:484 (Sept.) 1928.

made (figs. 1 and 2). The opaque medium was irregularly distributed in pools and scattered irregularly in thin layers over the surface of the heart. The sac was not obliterated at this time. On the twenty-ninth postoperative day physiologic solution of sodium chloride was substituted for surgical solution of chlorinated soda as the irrigating fluid. On the thirtieth postoperative day ascites, and within a few days generalized anasarca and hydrothorax, were found on physical and roentgen examination.

Without specific therapy either for the edema or for the cardiac condition, a spontaneous, rapidly increasing urinary output began five weeks after the onset of these symptoms. Simultaneously, the evidences of polyserositis diminished, and symptomatic improvement progressed uneventfully, so that the patient was able to leave the hospital ten weeks after his admission and seven weeks after the onset of ascites. free from symptoms. He is symptom-free at the time of writing.

PROGNOSIS AND COMPLICATIONS

Stewart¹⁷ reported subsequent observations in three cases of wounds of the heart. In the first case a 20 year old Negro suffered severe pain and dyspnea at the time of receiving the wound and in the hospital. The left lung was collapsed, and the anterior wall of the left ventricle was wounded. The coronary artery was wounded during operation and had to be ligated. Four years later (1908) the patient was symptom-free. Tuberculous inguinal adenitis occurred in the interim, and the patient died five years after injury (1909) from pulmonary tuberculosis. At autopsy obliterative pericarditis was observed. The heart weighed 370 Gm., and the old scar in the right ventricle was recognized. In the second case the patient was symptom-free after four years, and in case 3 the patient, seen two years after injury, did not complain of symptoms.

Hesse,¹⁸ in an exhaustive summary and analysis of one hundred and nineteen cases of wounds of the heart (twelve from his own hospital) in which the patients survived operation, concluded that in 77.3 per cent of the instances complete restitution of function was obtained and that in 22.7 per cent fair results and in 1.7 per cent poor results were seen. One patient died as a result of the pathologic condition, but only after complete recovery from the wound, and the author considered that the adhesive pericarditis which generally appears after operative intervention is the primary cause of the dysfunction that may occur. In the series of cases in which recovery took place, persons experienced attacks of pneumonia, measles, grip, etc., during epidemics, hard work, war.

17. Stewart, F. T.: *Ann. Surg.* **58**:67, 1913.

18. Hesse, E.: *Deutsche Ztschr. f. Chir.* **190**:239, 1925.

a hobo existence and a state of chronic alcoholism without apparent cardiac symptoms. The author emphasized the fact that ligation of the descending branch of the left coronary artery and its branches does not influence the end-results. The end-results are somewhat poorer in cases that are complicated by purulent pericarditis, but even in these instances complete recovery is not uncommon and the working capacity is frequently large. Adhesive pericarditis and mediastinopericarditis resulted in two cases with ultimate death from cardiac insufficiency.

Urrutice and Zamora¹⁹ reported an instance of stab wound of the heart in a 19 year old man, who complained of precordial pain one month after operation, and when seen two years later, still complained of precordial pain and dyspnea.

Jones²⁰ reported a case in which a stab wound of the left ventricle was sutured, presumably without anesthesia as the patient was unconscious when operated on. Six months later the patient complained of occasional moderate precordial pain and dyspnea on exertion, and the heart rhythm was disturbed.

Brunetti²¹ reported a case of aneurysm near the apex of the left ventricle resulting from a stab wound of the heart.

Rufanov²² reported the result of suture of a stab wound of the heart after twenty-eight years, performed with the patient under chloroform anesthesia. No ill effects, in the form either of pain or of impairment of cardiac efficiency, were noted.

COMMENT

From the standpoint of electrocardiographic changes resulting from wounds on the anterior surface of the heart, the picture varies but little from case to case, regardless of the presence or absence of involvement of the large coronary vessels or of the region of the anterior surface of the ventricle damaged. The primary change is a rise in the take-off of the T wave with a gradual return to the iso-electric line, accompanied by inversion of the T wave within ten days. In the vast majority of cases the final complete return of a normal curve is observed. One is forced to conclude that the electrocardiographic changes noted are, as is the generally accepted opinion, purely myocardial in origin and are dependent on the degenerative changes that occur in the muscle fibers involved.

The rarity of pain at the time of injury or subsequent to it, as well as the complete absence of pain during operation in the cases in which

19. Urrutice, C., and Zamora, M. A.: *Bol. de cir. de Chile* **10**:350, 1932.

20. Jones, J. F.: *Ann. Surg.* **65**:120, 1917.

21. Brunetti, L.: *Riv. d. radiol. e fis. med.* **4**:669, 1932.

22. Rufanov, I. G.: *Zentralbl. f. Chir.* **58**:3138, 1931.

only local anesthesia was used, supports the theory that the pain of cardiac origin is due to changes occurring only in the presence of intact muscle. It might be explained as being due to stretching of the cardiac muscle fibers or, in other words, to local dilatation of the myocardium. The possibility that anoxemia of the muscle fibers causes the pain cannot be discarded. The actively functioning intact muscle presumably becomes anoxic sooner than the divided muscle under similar circumstances.

Recently, Pickering and Hess,²³ in their work on the mechanism of headache, concluded that the sensory fibers of the meninges are located in the perivascular tissues and are affected by vascular tension. The possibility that a similar mechanism is present in the heart should be investigated.

With regard to the polyserositis which complicated our case, apparently as a result of the use of surgical solution of chlorinated soda or of the infection or of both, several points should be emphasized. If mere scarring of the pericardial sac were the only factor, spontaneous recovery would have to be explained by stretching of the scar tissue. Scar tissue tends to contract, and therefore one would expect a recurrence of the syndrome at some future time.

One year after the injury in Cox' case and five months after operation in our case there has been no recurrence of symptoms. The inflammation per se might induce these changes by direct reflex effect. Furthermore, the roentgenograms made after injecting an iodized and chlorinated peanut oil into the pericardial sac only two days prior to the onset of the clinical symptoms disclosed only moderate obliteration of the sac, with but little involvement about the base of the heart.

The reduction of pericardial capacity may have resulted from encroachment on the space by loculated or excessively thick exudate or by local edema. Such processes would have resolved in the course of healing of the inflammation, thus accounting for the return of adequate pericardial capacity.

However, this mechanical conception of the pathogenesis of polyserositis fails to explain the occurrence of encapsulated fluid in the right pleural cavity in our case and the usual observation of proliferative inflammation of the capsules of the liver and spleen seen at autopsy in this condition. The inflammatory reaction, though primary in the pericardial sac, also develops in other serous membranes. This might come about by lymphatic dissemination of bacteria, bacterial toxins or a chemical such as surgical solution of chlorinated soda. The primary lesion in the pericardium then becomes a focus from which the inflammatory agent, whether bacterial, toxic or chemical, is disseminated to the other serous membranes with the resultant serositis involving the

23. Pickering, G. W., and Hess, W.: Clin. Sc. 1:77, 1933.

pleura and abdominal membranes. The localization of the peritoneal involvement in the upper part of the abdomen, i. e., in the capsule of the liver and spleen, speaks strongly in favor of this view. The general subcutaneous anasarca, especially pronounced in the head, neck, upper extremities and chest, must be explained by venous obstruction.

These points can be settled only by further careful experimental observations along the lines of the experiments reported by Beck.

Finally, the circumstances under which the operation was performed with complete recovery serve to emphasize the fact that cardiac tamponade is a condition of extreme emergency. Whether it would have been better to aspirate the pericardial sac in this case, thus decompressing the sac and perhaps allowing more time for preoperative preparation, is problematic. At any rate, it is apparent that even with the heart at complete standstill the life of the patient may still be saved. And with this primary purpose in mind, sterility and the possibility of subsequent post-operative complications have to be disregarded.

SUMMARY

A case of stab wound of the heart with recovery is reported.

Complete electrocardiographic studies and their comparison with similar studies show that a Pardee curve, replaced after about ten days by an inversion of the T wave, occurred in all cases. A complete return to the normal curve is the rule.

Our case was complicated by polyserositis, which may have resulted from the use of surgical solution of chlorinated soda in irrigating the pericardial sac after the development of pericarditis. The mechanism of the development of polyserositis is discussed.

Roentgenographic visualization of the pericardial sac after injection of an iodized and chlorinated peanut oil was carried out. The pictures disclosed little obliteration of the pericardial sac.

The operation performed without anesthesia or anything more than the most cursory attempts at sterility, necessitated by the extreme state of the patient, resulted in ultimate and complete recovery.

INFECTION AND HEMORRHAGIC NEPHRITIS

WALTER L. WINKENWERDER, M.D.

NEIL McLEOD, M.D.

AND

MYLES BAKER, M.D.

BALTIMORE

Infection as a cause of diffuse hemorrhagic or glomerular nephritis is well known. Since Loehlein's¹ (1907) and Fahr's² (1912) fundamental observations emphasizing the frequency with which glomerular nephritis is associated with streptococcic infections, usually of the upper respiratory tract, subsequent extensive studies,³ both clinical and experimental, have tended to confirm these observations.

Longcope and his associates⁴ (1927) published the results of detailed clinical and bacteriologic studies of forty cases of acute and subacute glomerular nephritis. The onset of an overwhelming majority of the cases in their series (85 per cent) was accompanied or preceded by acute infections of the upper respiratory tract, of which 68.7 per cent showed the beta type, and 12.2 per cent the alpha type, of the hemolytic streptococcus. After years of observation they concluded that disappearance of infection and of the hemolytic streptococcus was related to recovery in nephritis and, contrariwise, that persistence of

This study was aided by a grant from the Ella Sachs Plotz Foundation.

From the Medical Clinic, School of Medicine, Johns Hopkins University and Hospital.

1. Loehlein, M.: Ueber die entzündlichen Veränderungen der Glomeruli menschlichen Nieren und ihre Bedeutung für die Nephritis, Leipzig, S. Hirzel, 1907 (forms pt. 4 of Arb. a. d. path. Inst. zu Leipzig, 1907); Ueber Nephritis nach dem heutigen Stande der pathologisch-anatomischen Forschung, *Ergebn. d. inn. Med. u. Kinderh.* **5**:411, 1910.

2. Fahr, T. Z.: Können wir die Nierenkrankungen nach ätiologischen Gesichtspunkten einteilen? *Virchows Arch. f. path. Anat.* **220**:277, 1912.

3. Bell, E. T.; Clawson, B. J., and Hartzell, T. B.: Experimental Glomerular Nephritis, *Am. J. Path.* **1**:247, 1925. Kollert, V.; Suchanek, E., and Singer, S.: Grundlagen der ätiologischen Behandlung der Nierenentzündungen, Leipzig, Franz Deuticke, 1929. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1930. Munk, F.: Die Nierenkrankheiten, ed. 2, Berlin, Urban & Schwarzenberg, 1925. Gray, J.: Causes and Sequences in Nephritis, *J. Path. & Bact.* **31**:191, 1928. Lichtwitz, L.: Praxis der Nierenkrankheiten, Berlin, Julius Springer, 1925. Van Slyke, D. D.; Stillman, E.; Moller, E.; Ehrich, W.; McIntosh, J. F.; Leiter, L.; MacKay, E. M.; Hannon, R. R.; Moore, N. S., and Johnston, C.: Observations on the Courses of Different Types of Bright's Disease and on the Resultant Changes in the Renal Anatomy, *Medicine* **9**:257, 1930.

4. Longcope, W. T.; O'Brien, D. P.; McGuire, J.; Hansen, O. C., and Denny, E. R.: Relationship of Acute Infections to Glomerular Nephritis, *J. Clin. Investigation* **5**:7, 1927.

infection and of the streptococcus was related in some way to progression of the disease.

Our purpose in the present communication is to report in detail an analysis of the various relationships between infection by *Streptococcus haemolyticus* and hemorrhagic nephritis. The data presented are based on a study of seventy-eight cases of hemorrhagic nephritis made by Dr. Longcope and a group of his associates over a period of nine years (including the series reported in 1927). For convenience in the presentation of the material the seventy-eight cases have been divided into three groups according to the status of the disease: group 1, hereafter termed the "well group," cases in which no evidence of the condition remains; group 2, hereafter termed the "latent group," cases in which it is latent; group 3, hereafter termed the "progressive and fatal group," cases in which it is progressive and chronic and those in which it has terminated fatally. A chart of each group illustrates the entire course of the disease in each patient. The essential criteria making this division possible were based on the correlated results of all the methods of study mentioned in subsequent sections of this paper. The proper status of the majority of the cases has undoubtedly been determined, but in several instances, especially in the latent group, a reshuffling may eventually be necessary, since in several of the cases which have been followed for a year or less the patients may become well or, on the contrary, their condition may progress imperceptibly to a chronic stage. With few exceptions, the patients classified (according to the criteria of Addis⁵) as either well or in the latent phases of nephritis were seen within a few days to a few weeks after the apparent onset of their disease, while a few acquired the disease while they were under observation. On the other hand, several of the patients whose nephritis was in the progressive stage or had terminated fatally were seen months and sometimes years after the alleged onset. Periodically, also, the majority of the patients were readmitted to the hospital for completion of various tests of renal function, including the dilution and concentration test of Volhard,⁶ the phenolsulphonphthalein test, the urea clearance test of Van Slyke⁷ and the quantitative estimation of the formed elements in the urine as described by Addis.⁸ The accessory nasal sinuses were always examined, and operative procedures were performed by Dr. Crowe and his staff.

5. Addis, T.: A Clinical Classification of Bright's Disease, *J. A. M. A.* **85**:163 (July 18) 1925.

6. Volhard, F., in von Bergmann, G., and Staehelin, R.: *Handbuch der inneren Medizin*, ed. 2, Berlin, Julius Springer, 1931, vol. 6.

7. Moller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies of Urea Excretion: Relation Between Urine Volume and Rate of Urea Excretion by Patients with Bright's Disease, *J. Clin. Investigation* **6**:485, 1928.

8. Addis, T.: The Number of Formed Elements in the Urinary Sediment of Normal Individuals, *J. Clin. Investigation* **2**:409, 1925.

FORMS OF INFECTION OBSERVED AT THE ONSET OF HEMORRHAGIC OR GLOMERULAR NEPHRITIS

The various forms of infection noted at the onset of nephritis are shown in table 1. Infections of the upper respiratory tract comprised 67.6 per cent of the total number, with tonsillitis the most frequent by far (44 per cent). With the exception of the small number (two) of cases of scarlatinal nephritis in this series, the frequency of infections of the upper respiratory tract agreed in general with data presented on other large series of cases of glomerular nephritis, and only a few of the other infections justify further comment.

Bronchitis was noted in six cases (1, 20, 21, 22, 38 and 57). In two of these cases (1 and 57) infection of the upper respiratory tract

TABLE 1.—*Forms of Infection Observed at the Onset of Seventy-Seven Cases of Hemorrhagic Nephritis, and the Frequency of Each in the Series*

Form of Infection	Frequency	Percentage
Tonsillitis and pharyngitis.....	41	44
Sinusitis.....	14	15
Pharyngitis.....	8	8.6
Bronchitis.....	6	6.5
Pneumonia.....	6	6.5
Scarlet fever.....	2	2.1
Abscess.....	2	2.1
Typhoid fever.....	1	1.1
Erythema.....	1	1.1
Subacute bacterial endocarditis.....	1	1.1
Rheumatic fever.....	4	4.3
Otitis media.....	1	1.1
Latent syphilis.....	6	6.5
Total.....	92	100

was not observed; in the other four the bronchitis was associated with, and undoubtedly was secondary to, tonsillitis, sinusitis or pharyngitis.

Pneumonia was observed in six cases (13, 15, 46, 51, 72 and 78). Patients 72 and 78 came under observation several months after the onset of their nephritis and therefore were inappropriate for analysis. Considerable doubt has recently been thrown on the previously accepted occurrence of hemorrhagic nephritis in pneumococcic pneumonia; hence the determination of the etiology of the pneumonia in the remaining four cases was important. Although Blackman, Brown, and Rake⁹ produced the pathologic changes characteristic of acute and subacute nephritis in rabbits by intravenous injections of an autolysate prepared from *Pneumococcus*, type I, as well as by intradermal injections of virulent strains of the same organism, postmortem investigation

9. Blackman, S. S.; Brown, J. H., and Rake, G.: The Production of Acute Nephritis by Means of a Pneumococcal Autolysate, *Bull. Johns Hopkins Hosp.* 48:74, 1931.

by Blackman and Rake¹⁰ in human beings revealed that apparently the occurrence of acute glomerular nephritis is limited to infants suffering from chronic pneumococcic infection, such as empyema, organizing pneumonia or pericarditis. In older children or adults no such changes were observed. Furthermore, in thirty-two cases of lobar pneumonia, also studied pathologically, not a single instance of diffuse nephritis was found. MacCallum,¹¹ Aschoff¹² and Fahr¹³ have referred to the development of acute nephritis in lobar pneumonia. None of the four cases of pneumonia in this series could be definitely attributed to the pneumococcus, as the following brief abstracts indicate:

CASE 13.—The patient had chronic tonsillitis, bronchopneumonia and nephritis on admission to the hospital. Hemolytic streptococcus, beta type, was cultured from both the sputum and the pharynx. Pneumococci were never found.

CASE 15.—The patient had a chronic cough for three weeks. On admission there was consolidation of the upper right lobe, chronic tonsillitis, chronic rheumatic endocarditis (apparently quiescent) and hemorrhagic nephritis. No sputum was ever obtained for culture; the pneumococcus was not found in cultures from the throat. Cultures of the blood were negative. Hemolytic streptococcus, beta type, was grown from the surface of the tonsils and from the ground-up tonsils after tonsillectomy.

CASE 46.—The patient was comatose on admission to the hospital following repeated generalized convulsions of several days' duration. There were marked anasarca, oliguria and nitrogen retention. Death occurred before adequate examination or cultures of the throat were made. Postmortem examination revealed acute sinusitis and lobular pneumonia; *Staphylococcus aureus* was grown from the former, but *Str. hemolyticus*, beta type, from the lungs; pneumococci were never found.

CASE 51.—The patient had three attacks of rheumatic fever prior to admission, the last beginning eight days before admission. Edema appeared two days before admission, when the patient presented chronic rheumatic endocarditis, hypertension, great anasarca, pronounced anemia, bronchopneumonia of the right lower lobe and urinary sediment characteristic of severe nephritis. Pneumococcus, type II, and *Str. haemolyticus*, beta type, were cultured from the sputum; this streptococcus was also obtained repeatedly from the tonsils and pharynx. The presence of both organisms prevented assigning definite etiologic significance to either.

The striking rarity of infections other than those of the respiratory tract was so evident that little comment seems necessary. It is interesting, however, that acute nephritis of rather severe form developed during

10. Blackman, S. S., and Rake, G.: Acute Pneumococcal Nephritis, *Bull. Johns Hopkins Hosp.* 51:217, 1932.

11. MacCallum, W. G.: *A Textbook of Pathology*, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 267.

12. Aschoff, Ludwig: *Pathologische Anatomie*, ed. 4, Jena, Gustav Fischer, 1919, p. 521.

13. Fahr, Theodore, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1929, vol. 5. pt. 2, p. 285.

the course of typhoid fever in one patient (case 33), who is now in the latent phase of the disease. Heavy albuminuria and cylindruria characterized the urinary sediment; only an occasional red blood cell was found. The ultimate clinical course excluded the possibility of pyelitis as a cause of the urinary changes. Chronic tonsillitis coexisted, however, and hemolytic streptococci, beta type, were grown in small numbers; following an exacerbation of the tonsillar infection they grew abundantly. Whether the nephritis was caused by the streptococcus or by the typhoid infection is uncertain; but in view of the character of the urinary abnormalities it seems possible that the nephritis in this case was produced by the typhoid fever.

In view of the recent statement of Coburn¹⁴ and many others that *Str. haemolyticus* is related etiologically to rheumatic fever, the association of rheumatic fever with only four cases of hemorrhagic nephritis in this series is highly interesting. Goldring,¹⁵ employing the technic of Addis, showed that the urine in many cases of acute rheumatic fever contained abnormally large numbers of red blood cells; in pneumonia and myocardial insufficiency, no such changes were noted. The association of acute hemorrhagic nephritis with acute rheumatic fever was noted and described by Goldring,¹⁶ Loeb¹⁷ and Coburn.¹⁸ The latter attributed the urinary changes, which simulated ordinary acute nephritis, to hemorrhage in common with other hemorrhagic phenomena, such as epistaxis and purpura, which occur during what he termed "the third phase in the evolution of the rheumatic process." The urinary sediment is characterized chiefly by hematuria and minimal cylindruria, although one of Goldring's and one of Loeb's patients exhibited large amounts of albumin. Pronounced renal insufficiency may supervene. If the view that *Str. haemolyticus* is responsible for rheumatic fever and also for hemorrhagic nephritis is true, it is curious that despite the close and not infrequent association of what appears to be hemorrhagic nephritis with acute rheumatic fever the antithesis, or development of rheumatic fever during the course of acute diffuse nephritis, as presented here, did not occur in this series. Only in case 51 did it appear

14. Coburn, Alvin F., and Pauli, R. H.: Studies on Relationship of the Streptococcus *Haemolyticus* to the Rheumatic Process, *J. Exper. Med.* **56**:609, 1932.

15. Goldring, W., and Wyckoff, J.: Studies of the Kidney in Acute Infections: Observations with the Urine Sediment Count (Addis) in Acute Rheumatic Fever, *J. Clin. Investigation* **8**:569, 1930.

16. Goldring, W.: Occurrence of Diffuse Glomerulonephritis in Acute Rheumatic Fever, *M. Clin. North America* **14**:1551, 1931.

17. Loeb, R. F.: Unusual Manifestations of Rheumatic Fever in Relation to Newer Concepts of This Disease, *M. Clin. North America* **4**:1540, 1931.

18. Coburn, Alvin F.: Relationship of the Rheumatic Process to the Development of Alterations in Tissues, *Am. J. Dis. Child.* **45**:933 (May) 1933.

likely that nephritis developed during an exacerbation of the rheumatic process. No definite rheumatic manifestations other than quiescent endocardial lesions were noted at the onset of the nephritis in the other three cases, notwithstanding the fact that infections of the upper respiratory tract associated with hemolytic streptococci, beta type, had occurred.

INCIDENCE OF STR. HAEMOLYTICUS IN HEMORRHAGIC NEPHRITIS

The bacteriologic studies presented here regarding the incidence of Str. haemolyticus in the infections associated with hemorrhagic nephritis represent, with few exceptions, the results of cultures made as soon as observations were begun and periodically thereafter throughout the course of the disease. If a causal relationship between infections due to the hemolytic streptococcus and nephritis is presumed, the evidence desirable and, indeed, necessary to strengthen this presumption must be derived from bacteriologic observations made not only at the onset

TABLE 2.—*Incidence of Hemolytic Streptococcus in Seventy-Eight Cases of Hemorrhagic Nephritis*

Type of Organism	Well Group	Latent Group	Progressive and Fatal Group	Total
Beta.....	21	17	24	62
Alpha.....	0	0	5	5
No organisms.....	1	3	7	11

but also during the later phases of the disease. The organism should be present during the initial stages or during the chronic stages of the disease, if the latter develop; and, contrariwise, if the patient recovers from nephritis, it is reasonable to assume that the hemolytic streptococci should disappear.

The majority of the patients who recovered or in whom the condition became latent came under observation during the acute or active stage of infection, and cultures were obtained periodically, in most instances, in these two groups throughout the entire course of the disease. In contrast, in the group in which the disease proved progressive or fatal, several patients presented themselves weeks, months and occasionally years after the onset. Bacteriologic data on the latter group are nevertheless of importance, since owing to the assiduity with which focal infection was attacked when the condition of the patient permitted, chronic infection in the well group and the group in which the disease became latent proved relatively infrequent. The cultural findings, therefore, though not comparable in the three groups, are complementary.

Table 2 illustrates the incidence of the hemolytic streptococcus in the three groups of cases, irrespective of the stage of nephritis. Sixty-seven cases, or 92 per cent. showed the beta type; five, or 8 per cent. all

progressive or fatal, showed the alpha type (alpha prime). The beta type was recovered on only two occasions in these five cases, but in such small numbers as to be considered of relative unimportance. In eleven cases, designated as showing "no organisms" in charts 1, 2 and 3, neither type of the streptococcus was obtained.

Table 3 illustrates further the incidence of *Str. haemolyticus* in the active or initial phase of nephritis, compared with the incidence when it became eventually possible, in the course of the disease, to divide the entire series into the three groups: well, latent, and progressive or fatal. The point of interest in the table is the high percentage of positive cultures obtained during the active stage in the well and latent groups as compared with the sharp decrease in positive cultures when the

TABLE 3.—*Incidence of Hemolytic Streptococcus During Successive Stages of Nephritis*

Group	Active Stage			Well, Latent and Progressive Stage		
	Str. Haemo-lyticus	Incidence	Per-centage	Str. Haemo-lyticus	Incidence	Per-centage
Well group..... (22 cases)	+	20	90	+	7	32
	0	2	10	0	15	68
Latent group..... (20 cases)	+	16	80	+	6	32
	0	4	20	0	13	65
				No culture	1	4.9
Progressive and fatal group... (36 cases)	+	19	73	+	19	63.3
	0	7	27	0	11	36.6
	No culture	10		Patient died in acute stage	6	

patients either recovered or entered the latent phase. Of these groups, 90 and 80 per cent, respectively, gave positive cultures during the active stage, but eventually organisms were no longer obtained in 68 per cent of both groups. In the group with progressive nephritis or dead, however, the incidence maintained a tenacious constancy: Seventy-three per cent gave positive cultures during the initial stage and 63 per cent during the progressive stage. Cultures were taken from twenty-six patients in the initial stage of nephritis: Nineteen gave positive cultures, and of these, six died during the early weeks of the disease, nine continued to harbor the organism during the chronic active stage and only four reverted to a negative state. Seven patients of this group gave consistently negative cultures throughout the entire course of their disease. Ten additional ones came under observation after the initial phase of the disease had passed, but cultures were positive and continued so throughout the period of observation. It is interesting to note that the five cases classified as due to streptococcic infections, alpha type, were all confined to the progressive group.

From the foregoing data one may conclude, therefore, that *Str. haemolyticus* is apparently related to successive phases of hemorrhagic nephritis, since this organism was recovered from the great majority of the patients in the active phase of the disease, and disappearance of this organism occurred in the majority of those who recovered or in whom the disease subsided to the latent stage, whereas persistence of the streptococcus was characteristic of the chronic stage of the disease. This relationship was established and emphasized by Longcope,⁴ and this analysis merely confirms his views.

THE CHARACTER OF INFECTIONS OBSERVED AT THE ONSET OF NEPHRITIS

An attempt to judge quantitatively the intensity of infections observed at the onset of nephritis is obviously difficult. This was especially true of many cases in this series, some of which were seen when

TABLE 4.—*Character of Infections Observed at Onset of Seventy-Seven Cases of Hemorrhagic Nephritis*

Character of Infections	Well Group (22 Cases)	Latent Group (20 Cases)	Progressive and Fatal Group (35 Cases)	Total
Acute.....	19 (85%)	19 (95.2%)	9 (25%)	47
Chronic.....	3 (15%)	1 (48%)	17 (50%)	21
No demonstrable infection.....	0	0	9 (25%)	9

the manifestations of acute infection were subsiding, or when, comparatively late in the disease, the evidence of chronic infection was questionable or seemed insignificant; in fact, in several cases infection was never demonstrated. However, differentiation between acute and chronic infection, irrespective of the factor of intensity, was possible, and in attempting the classification of the cases on this basis, as shown in table 4, two outstanding relationships were found.

Acute infection accompanied by definite constitutional symptoms occurred in forty-seven cases, or 61 per cent of the entire series. Of these, thirty-eight, or 80 per cent, were equally divided between the well and latent groups; only nine, or 20 per cent, were in the chronic or fatal group. In this series, therefore, hemorrhagic nephritis the onset of which was preceded or accompanied by acute infection with definite constitutional symptoms almost invariably pursued a favorable course. This observation suggests the presence of modifying factors other than the initial infection precipitating the nephritis which, preventing recovery, might have caused progression of the disease or death of the patient in the nine cases mentioned (44, 45, 51, 56, 57, 62, 69, 72 and 75). Detailed analysis of the records disclosed that such factors, namely, intercurrent infections, undoubtedly were the primary cause of

death in three fatal cases and of progressive nephritis in three other cases, as the following brief abstracts illustrate.

CASE 44.—The patient had severe hyperthyroidism of sixteen months' duration. Acute tonsillitis and pharyngitis developed while he was in the ward, followed in sixteen days by acute hemorrhagic nephritis. In the second week of the latter illness, accidental varicella infection was contracted, and death followed quickly.

CASE 45.—The patient had acute pharyngitis complicated by cervical adenitis and hemorrhagic nephritis. Drainage of the involved cervical glands revealed the presence of the hemolytic streptococcus, beta type. There was rapid development of multilobar pneumonia with bacteremia, caused by *Pneumococcus*, type IV; 15 colonies per cubic centimeter were counted in blood culture. The patient died on the fifth day of the latter infection.

CASE 51.—This case has already been abstracted (p. 300). Nephritis apparently occurred during the sixth day of an exacerbation of rheumatic fever. Pneumonia developed during the active stage of the nephritis; the latter became progressive without an intervening latent phase, and death followed in seven months.

CASES 56, 57 and 75.—The patients had recurring infections associated with severe exacerbations of nephritis which ushered in the progressive stage of nephritis.

In cases 44, 45 and 51, death was due, undoubtedly, to a combination of infections; it could not be attributed primarily to nephritis. In cases 56, 57 and 75, intercurrent infections probably caused progression of the nephritis. Only three cases (62, 69 and 72), then, in which nephritis followed severe acute infection became chronic for reasons not recognized.

In striking contrast to the favorable progress of hemorrhagic nephritis in which the onset was associated with acute infection accompanied by constitutional symptoms was the course of nephritis with which there was either chronic infection or, in some cases (nine), no demonstrable infection at all. Thirty cases, or 40 per cent of the series, belonged in this category; of these, twenty-six cases, or 85 per cent, were progressive or fatal; only three, or 10 per cent, resulted in recovery, and only one became latent. Some question arose as to the proper classification of these cases, seventeen of which were allocated to the "chronic infection" group, and nine to the "no infection" group (charts 1, 2 and 3, and table 4). All the patients denied having any symptoms or manifestations of acute infection at or directly preceding the onset of nephritis, and in five patients no infection was ever demonstrated while they were under observation. Some, however, came under observation months, or, in a few instances, years after the alleged onset of their disease, and on this basis one may justifiably doubt the accuracy of their histories; but because denial of infection was so constant and characteristic of patients in these groups, we were inclined to accept the histories as essentially accurate.

The cause of the nephritis in the five cases in which no obvious focus of infection was demonstrable is not clear. One must accept either the

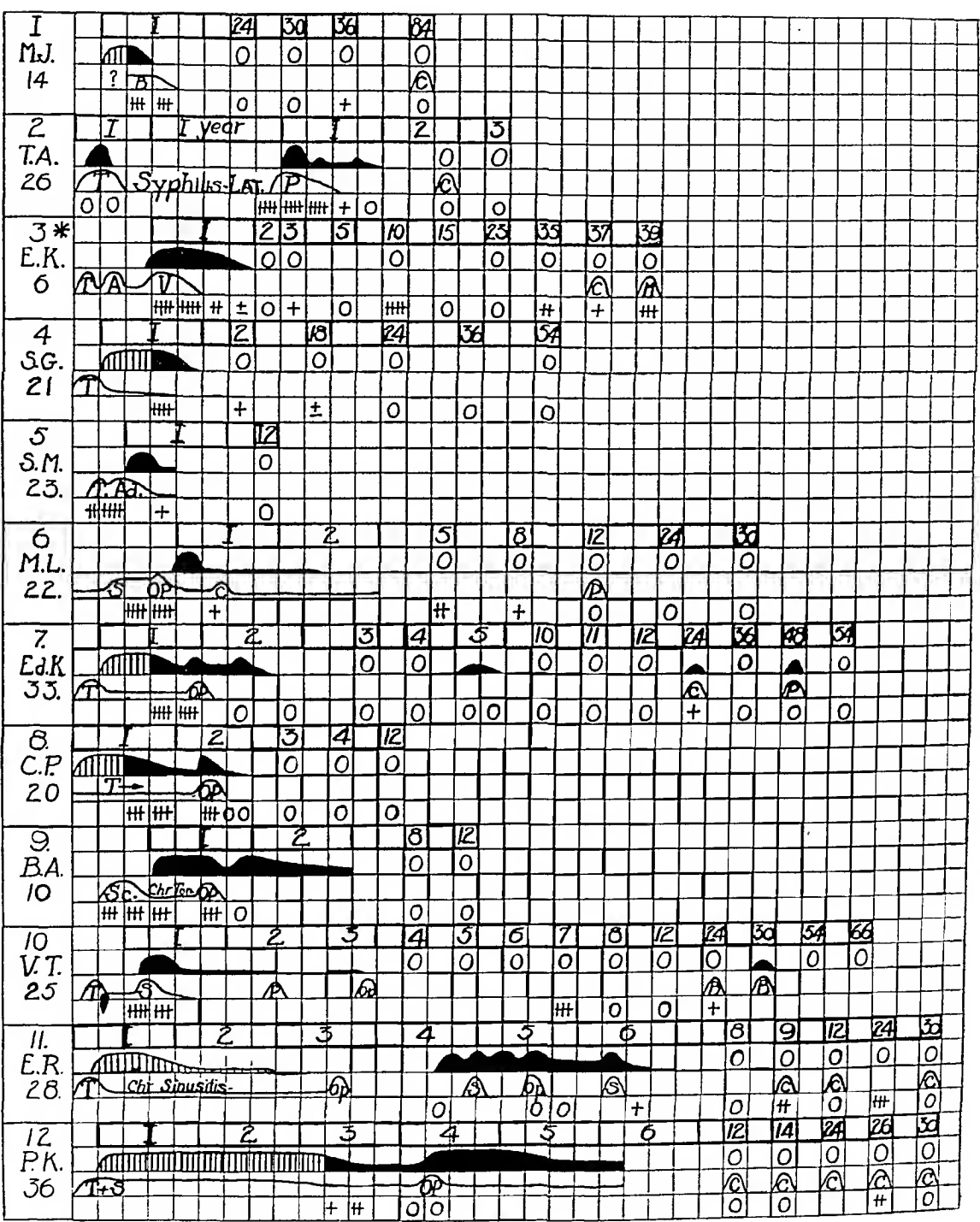


Chart 1.—Part 1.

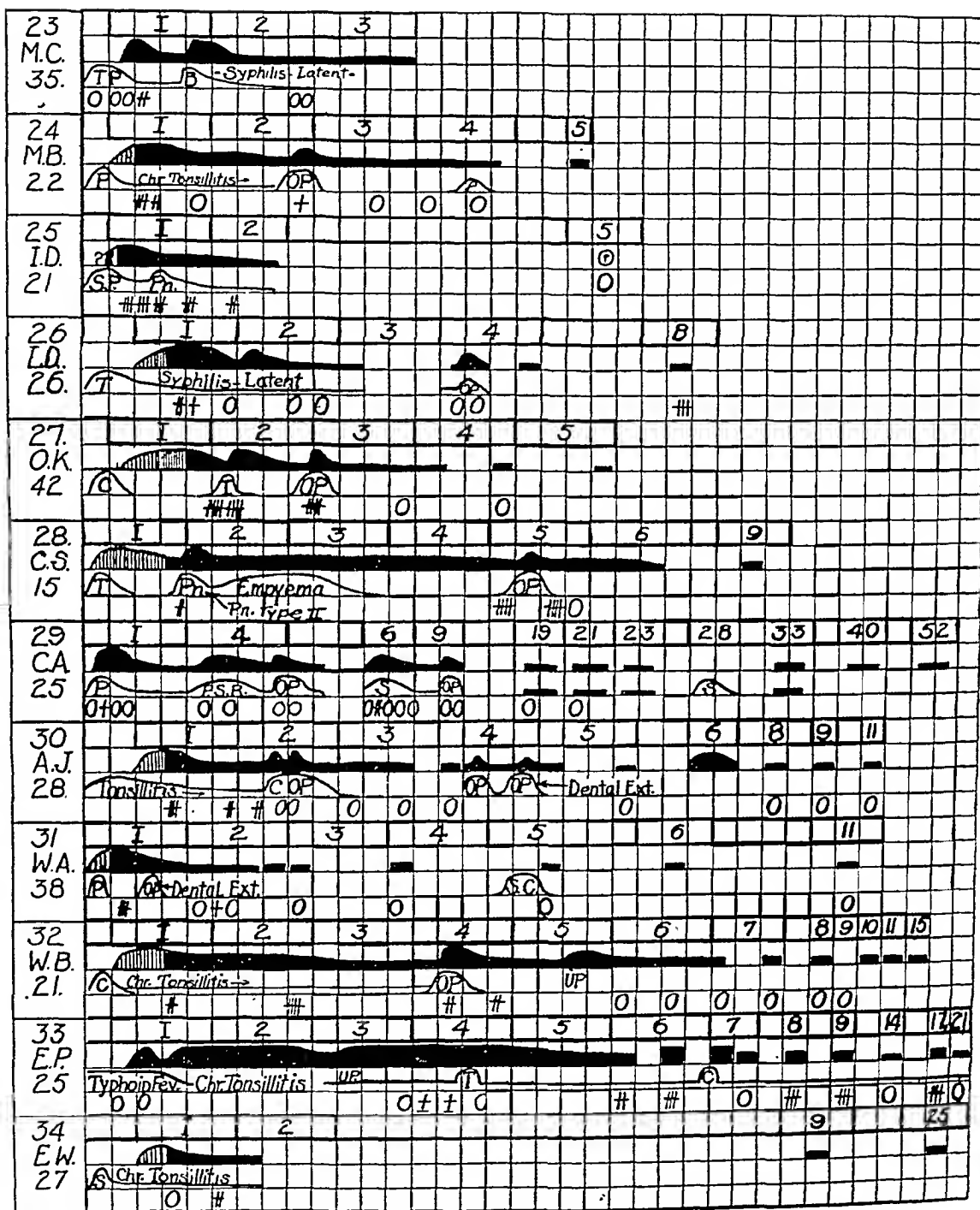


Chart 2.—Part 1.

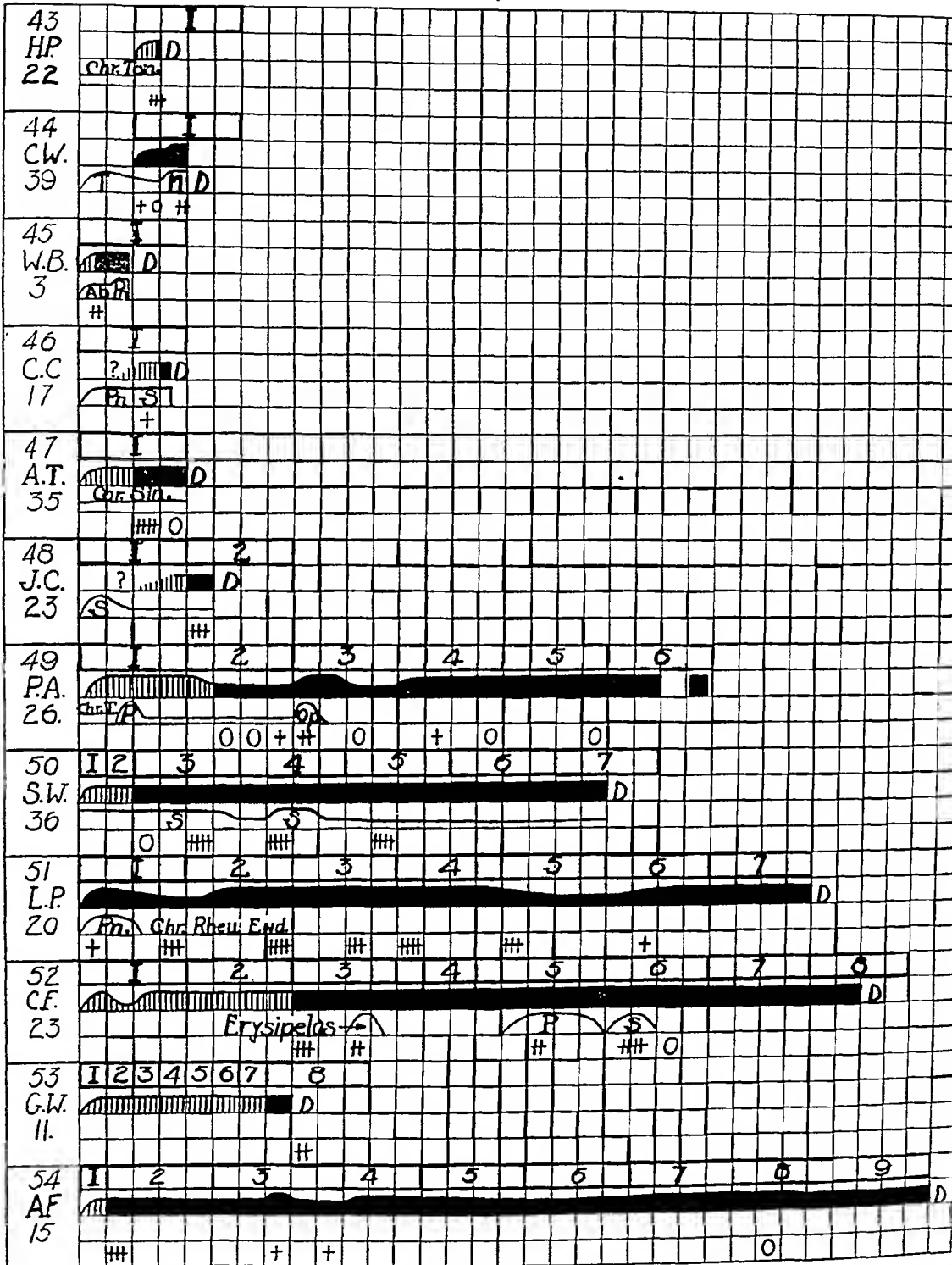


Chart 3.—Part 1.

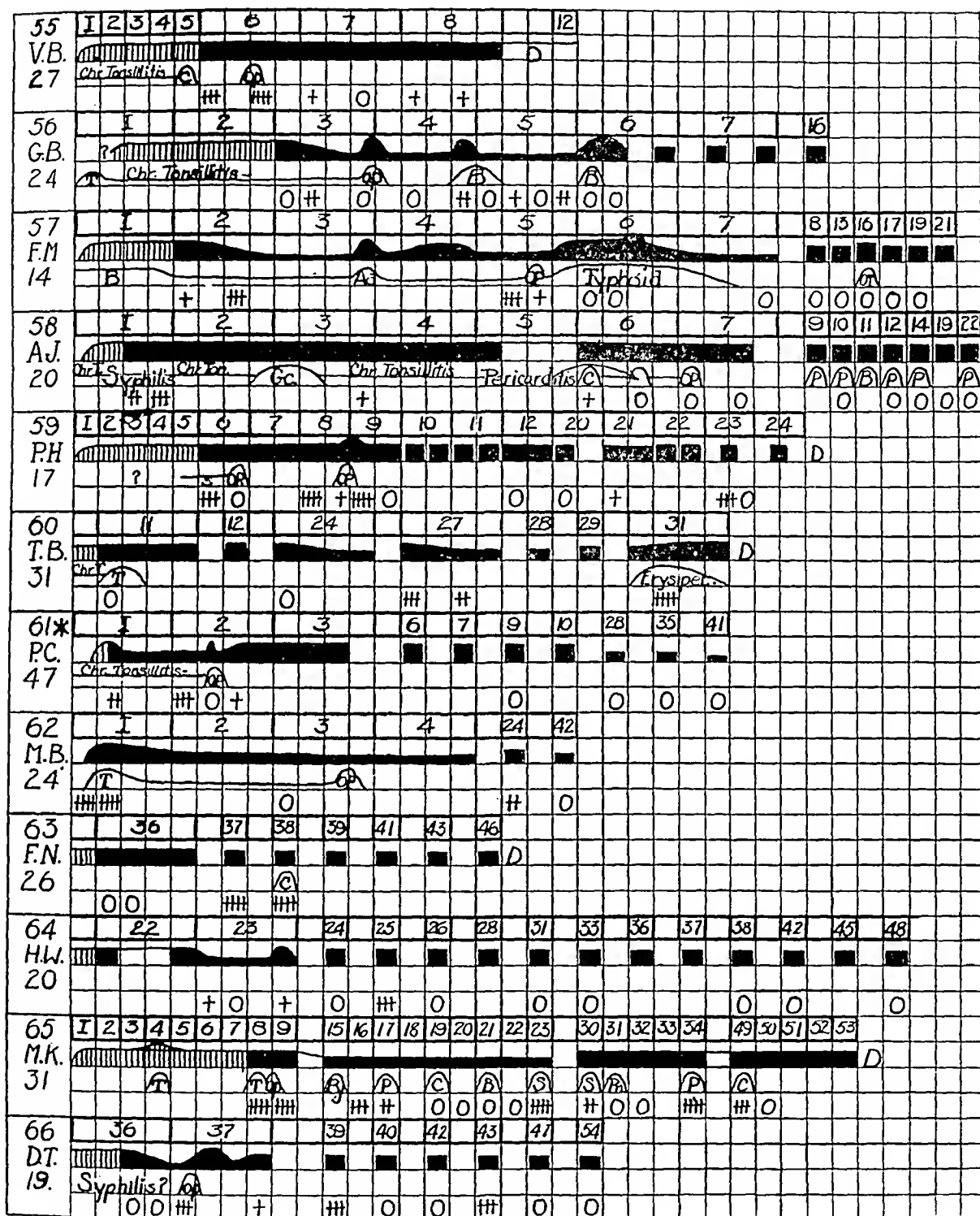


Chart 3.—Part 2.

Chart 3.—Progressive and fatal group. In cases 43 to 66 hemorrhagic nephritis was associated with the presence of *Str. haemolyticus*, beta type. In cases 67 to 71 hemorrhagic nephritis was associated with the alpha type of the hemolytic streptococcus. In cases 72 to 78 no micro-organisms were demonstrated.

*Now in latent stage of hemorrhagic nephritis.

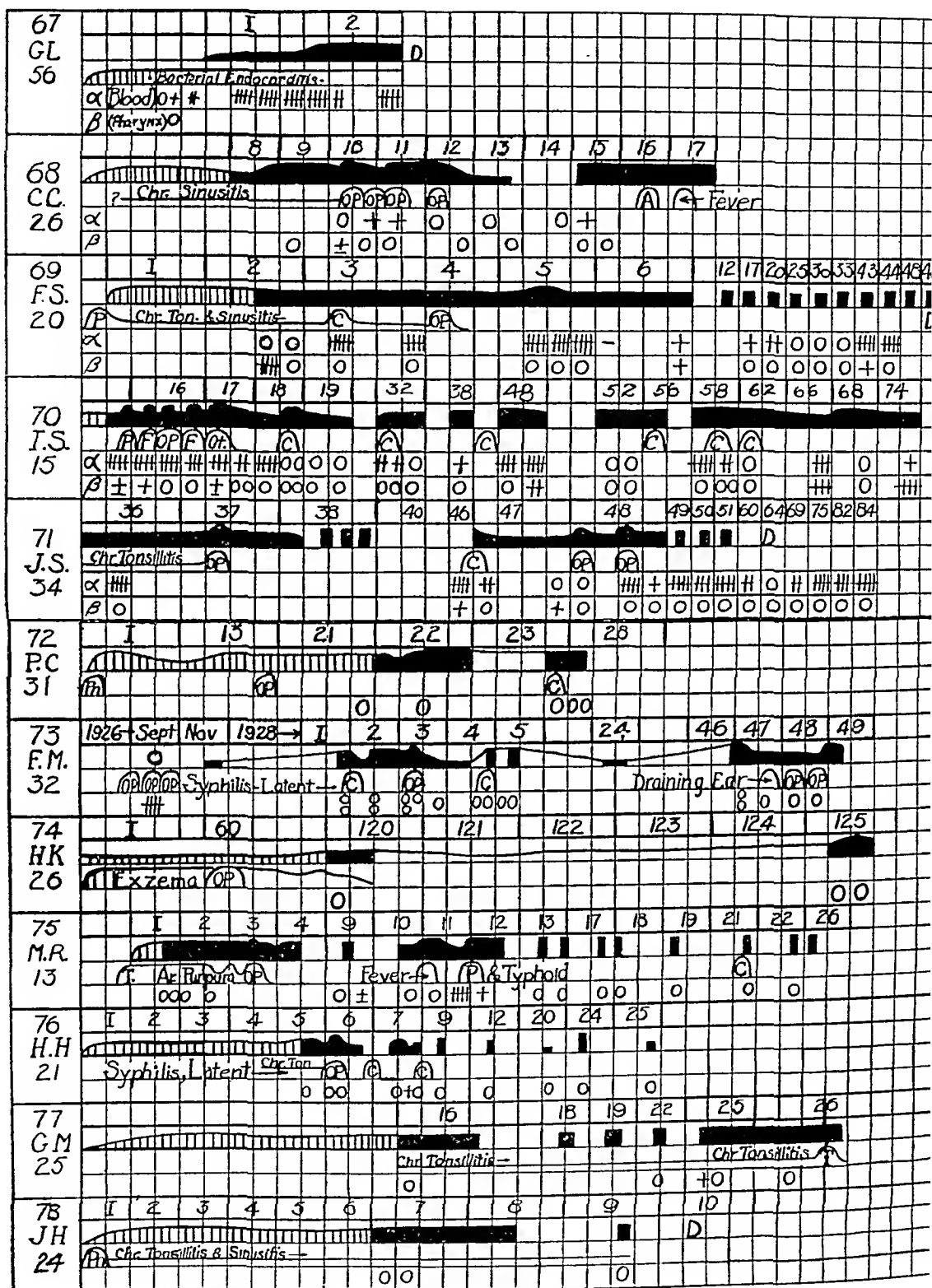


Chart 3.—Part 3.

view that the infections were too mild to attract attention, or the view that nephritis developed without the impetus of infection and was due to causes still unknown.

The possible underlying relationships between acute infection and chronic infection noted at the onset and the ultimate course of nephritis will be discussed later in greater detail.

THE PRODROMAL PERIOD: THE TIME INTERVAL BETWEEN THE ONSET OF INFECTION AND THE ONSET OF HEMORRHAGIC NEPHRITIS

A definite interval of time between the onset of infection and the manifestations of hemorrhagic nephritis in scarlatina has long been recognized. The usual length of this period in scarlet fever, as given by Schick¹⁹ and Goodall,²⁰ is from three to four weeks. It is also well known that a similar period can usually be demonstrated²¹ in cases of hemorrhagic nephritis following infections other than those associated with scarlatina. In this series, only forty-one cases in which acute infec-

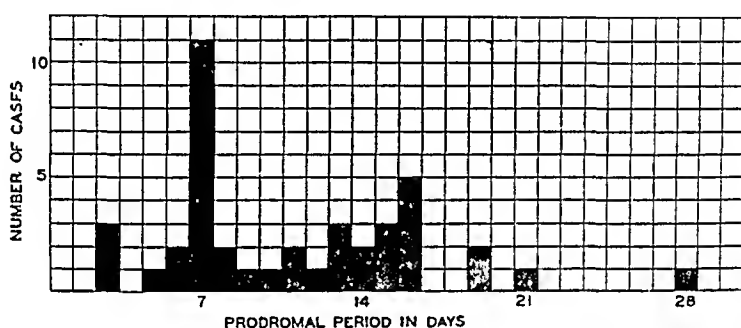


Chart 4.—The prodromal period in hemorrhagic nephritis. This shows the prodromal period in forty-one cases of hemorrhagic nephritis. The ordinates represent the numbers of cases and the abscissas the numbers of days. The prodromal period varied between three and twenty-eight days; the most frequent was seven days, and the average was ten and nine-tenths days. Nephritis developed on or between the seventh and the sixteenth day in thirty-three cases (80 per cent).

tion preceded the onset of nephritis provided adequate data whereby the prodromal period could be determined.

Although the onset of infection and the manifestations of nephritis rarely appeared simultaneously, accurate calculation of the prodromal period was, at best, difficult, and the result represents, in most instances, a mere approximation; for unless the patient is examined carefully each day after the onset of infection, one cannot state definitely the day of onset of the nephritis. Of the forty-one cases, only six devel-

19. Schick, B.: Die Nachkrankheiten des Scharlach, *Jahrb. f. Kinderh.* **65**:132, 1907.

20. Goodall, E. W.: On the Aetiology and Clinical Aspects of Scarlatinal Nephritis, *Guy's Hosp. Rep.* **31**:91, 1899.

21. Longcope,⁴ Osman²² and Addis.²³

oped in the wards, where examinations of the urine were made daily. In the remaining thirty-five cases, the appearance of edema, oliguria or hematuria as noticed by the patient was assumed to mark the day of onset.

Nephritis appeared as early as the third day in three cases, and in one case as late as the twenty-eighth day; in the largest number of cases, eleven, it developed on the seventh day; the average for the whole group was ten and nine tenths days. In thirty-three cases, or 80 per cent of the entire group, the prodromal period fell on or between the seventh and sixteenth days. According to chart 4 there was a progressive decrease in the number of patients in whom nephritis developed during the third and particularly during the fourth week. These figures agree closely with those given by Osman and his co-workers²² for thirty-six cases of acute hemorrhagic nephritis but differ from the data given by Schick¹⁹ and Goodall²⁰ for postscarlatinal nephritis and by Addis²³ for hemorrhagic nephritis. In the series presented by Schick and Goodall, the onset of nephritis was noted more frequently during the third week, whereas the weekly frequency among Addis' cases was practically uniform, except for a slight decrease during the fourth week.

Six cases (2, 5, 6, 9, 22, and 44) were followed closely during the prodromal period in the wards, but the number was too small to serve as controls for the larger group of thirty-five cases. The prodromal period in these six cases varied greatly. The shortest was five and the longest nineteen days, with an average of twelve and three tenths days. The latter value was in close agreement with the average for the whole group.

DURATION OF ACTIVE INFECTION AT THE ONSET OF NEPHRITIS
CORRELATED WITH DURATION OF THE ACTIVE
STAGE OF NEPHRITIS

Table 5 suggests that there was a direct relationship between the duration of acute or active infection and that of the active phase of nephritis only in the group that went on to recovery; no such conditions apparently obtained in the group that became latent, although the average duration of the active phase in the two groups was approximately equal. Because of the presence of chronic infection in the progressive and fatal group, comparison of the duration of active infection with that of active nephritis was impossible, unless one considers progressive nephritis as the active phase in this type of Bright's disease.

22. Osman, A. A.; Close, K. G., and Carter, H.: *Studies in Bright's Disease: Observations on the Aetiology of Scarlatinal Nephritis*, *Guy's Hosp. Rep.* **83**:360, 1933.

23. Addis, T.: *Haemorrhagic Bright's Disease*, *Bull. Johns Hopkins Hosp.* **49**:271, 1931.

SEASONAL VARIATION IN THE ONSET OF HEMORRHAGIC NEPHRITIS

The onset of hemorrhagic nephritis, as represented in table 6, occurred more frequently during the fall, winter and spring months: fifty-four cases in the interval from September to April, inclusive, as compared with fifteen in the period from May to August. This seasonal variation coincided with waves of infections of the upper respiratory tract occurring in Baltimore, and this relationship became more

TABLE 5.—*Duration of Active Infection at Onset Correlated with Duration of Active Phase of Nephritis.**

Duration of Active Infection	Well Group		Latent Group	
	Cases	Duration of Active Phase of Nephritis, Weeks	Cases	Duration of Active Phase of Nephritis, Weeks
1 week or less.....	8	2.5	6	4.1
1 to 2 weeks.....	7	3.3	10	2
3 weeks or more.....	6	6	5	4

* Definite correlation between the duration of active infection and the duration of the active stage of nephritis was demonstrable only in the well group; the average duration of the latter period was approximately equal in both groups. Because of the presence of chronic infection in the progressive group a similar relationship could not be determined.

TABLE 6.—*Seasonal Variation in the Onset of Sixty-Nine Cases of Hemorrhagic Nephritis**

Month	Well Group	Latent Group	Progressive or Fatal Group	Total
January.....	2	1	..	3
February.....	2	4	2	8
March.....	3	5	3	11
April.....	3	3	2	8
May.....	1	1	2	4
June.....	1	..	4	5
July.....	1	1	2	3
August.....	1	1	1	3
September.....	..	3	..	3
October.....	1	..	3	4
November.....	5	1	2	8
December.....	1	1	7	9

* It was impossible to state accurately the month of onset in cases 47, 50, 63, 66, 67, 70, 71 and 74 (all of progressive group). The incidence was much greater during the fall, winter and spring months: fifty-four cases from September through April compared with fifteen cases during May and August. This variation was more noticeable in the well and latent groups.

pronounced if one excluded the progressive and fatal group, in which the relatively uniform monthly incidence was related, we believe, to the factor of chronic infection. In the majority of cases in this group nephritis apparently developed without the impetus of acute infection.

INFECTIONS OCCURRING DURING THE COURSE OF HEMORRHAGIC NEPHRITIS EXCLUSIVE OF THOSE AT THE ONSET OF THE DISEASE

Further analysis of the relationship of infection to the progress of nephritis in this series shows that exacerbations of the disease were

in most instances associated with infections of the upper respiratory tract, in which the incidence of *Str. haemolyticus* was considerably higher than in infections not associated with exacerbations of nephritis.

Difficulty often arises in determining exactly the occurrence of an exacerbation. This is particularly true in the progressive type of the disease wherein variations, although sometimes pronounced, are observed without any discernible cause. An exacerbation of nephritis when associated with overt infection appears usually within twenty-four hours after the infection begins. Case 23 (chart 2) illustrates the difference in duration between the prodromal period occurring prior to the onset of nephritis and that occurring prior to the beginning of an exacerbation. The former was thirteen days. By the twenty-ninth day of the disease, convalescence was apparently established, and the presence of nephritis was revealed only by traces of albumin and a few red blood cells in the urine. On the thirtieth day, acute bronchitis intervened and an exacerbation of the nephritis, marked particularly by a sharp increase of the hematuria, was noted within twenty-four hours. The hemolytic streptococcus, beta type, was recovered from the sputum in almost pure culture. In seven days, the fever, tachycardia, cough and physical signs of the infection had disappeared, and, coincidentally, the urine reverted to its original status. The duration of the prodromal period at the onset of acute nephritis was originally compared by Schick¹⁹ and Pirquet²⁴ with the similar period in the development of serum disease. There is considerable experimental evidence²⁵ to suggest that during this period a hypersensitive state may develop, which may account for some of the manifestations of streptococcic infection. On the basis of this analogy, we suggest that exacerbations of nephritis following acute streptococcic infections simulate

24. von Pirquet, C. E.: *Allergy*, *Arch. Int. Med.* **7**:259 (Feb.) 1911.

25. (a) Lukens, F. D. W., and Longcope, W. T.: *Experimental Acute Glomerulitis*, *J. Exper. Med.*, **53**:511, 1931. (b) Hansen-Pruss, O. C.; Longcope, W. T., and O'Brien, D. P.: *Skin Reactions to Filtrates of Haemolytic Streptococci in Acute and Subacute Nephritis*, *J. Clin. Investigation* **7**:543, 1929. (c) Derick, C. L., and Fulton, M. N.: *Skin Reactions of Patients and Normal Individuals to Protein Extracts of Streptococci*, *ibid.* **10**:121 (April) 1931. (d) Ophüls, W.: *The Aetiology and Development of Nephritis*, *J. A. M. A.* **69**:1223 (Oct. 13) 1917. (e) Bell, E. T.; Clawson, B. J., and Hartzell, T. B.: *Experimental Glomerular Nephritis*, *Am. J. Path.* **1**:247, 1925. (f) Kuczynski, M. H.: *Nephritisstudien*, *Virchows Arch. f. path. Anat.* **227**:186, 1920. (g) Duval, C. W., and Hibberd, R. J.: *Experimental Glomerular Nephritis Induced in Rabbits with the Endotoxic Principles of Streptococcus Scarlatina*, *J. Exper. Med.* **44**:567, 1926. (h) Lukens, F. D. W.: *Acute Experimental Glomerulitis Following Repeated Injections of Haemolytic Streptococci into the Renal Artery*, *Bull. Johns Hopkins Hosp.* **49**:312 (Nov.) 1931. (i) McLeod, N., and Finney, G. G.: *Acute Experimental Glomerulitis Following Injections of Streptococcus Viridans into the Renal Artery*, *ibid.* **51**:311 (Nov.) 1932.

an accelerated allergic reaction, such as that following the injection of horse serum into a subject already sensitized thereto. Definite alterations in the severity of nephritis also occur with other infections, such as pneumonia and typhoid fever, but whether such changes are exacerbations such as occur after streptococcic infections, as described, is doubtful, for by close study it was possible to show that the prodromal period following pneumonia or typhoid fever was longer and the increase in the urinary sediment was less abrupt. This difference was well illustrated in case 75, in which moderate increases in the formed elements of the urine occurred during the first two weeks of typhoid fever, but within thirty-six hours after the beginning of acute pharyngitis, due to *Str. haemolyticus*, beta type, a sharp increase in albumin and gross hematuria was noted. The changes in nephritis associated with pneumonia and typhoid fever were probably the manifestations of the usual mild renal irritation attendant on any febrile illness; but the sharp, abrupt change coincident with the streptococcic infection suggested a specific relationship between the streptococcic infection and the original cause of nephritis.

Exacerbations of nephritis, usually of a transient character, follow within twenty-four hours after operative procedures (tonsillectomies, adenoidectomies, dental extractions and antrectomies). These exacerbations are always manifested by increases in the urinary sediment, usually by oliguria, in some patients by slight increases in blood pressure, and less often by the increase or appearance of edema. The cause of this reaction cannot be stated definitely. It is not probable that the changes are due to the effect of the anesthesia. It is more likely that the mechanical manipulation of infected tissue may liberate toxic bacterial products sufficient to intensify the renal injury already present. Occasionally reactions after operation are so pronounced and so prolonged as to support the latter suggestion.

One hundred and twenty-six infections, tabulated in table 7, occurred during the course of the disease in this series. Infections of the upper respiratory tract comprised the majority: ninety-five, or 72 per cent. Forty-two infections were associated with exacerbations, and of these, 55 per cent were characterized by cultures positive for *Str. haemolyticus*, as compared with 30 per cent of the eighty-four infections not accompanied by exacerbations. These differences were not marked, but they indicated that when an infection is followed by exacerbation of nephritis *Str. haemolyticus* is likely to be found. Exacerbations of nephritis also occurred despite the failure to demonstrate any inciting factor. Of a total of sixty-three exacerbations in the entire series, forty-two, or 66 per cent, were associated with infections; the remaining twenty-one, or 34 per cent, were apparently unrelated to active infections.

In table 8, the total number of infections noted in each of the three groups of cases is correlated with the frequency of the streptococcus and of the exacerbations observed. It may be noted that 67 per cent of the infections inducing exacerbations of nephritis in the well group, and 50 per cent of those in the latent group, yielded the hemolytic streptococcus in culture, whereas only 32 per cent of the infections in the well

TABLE 7.—*Relationship of the Form of Intercurrent Infection to the Course of Nephritis, and of Str. Haemolyticus to Infections Causing Exacerbations*

Infection Observed During Course of Nephritis	Cases	Incidence of Str. Haemolyticus			Incidence of Exacerbations	Incidence of Str. Haemolyticus in Exacerbations		
		+	0	No Culture		+	0	No Culture
Infectious conditions accompanied by exacerbations of nephritis								
Coryza.....	41	15	21	5	9	4	4	1
Pharyngitis.....	21	8	8	5	6	3	2	1
Bronchitis.....	13	6	3	4	5	2	1	2
Sinusitis.....	9	7	2	..	3	2	1	..
Pneumonia.....	5	2	3	..	2	1	1	..
Unexplained fever.....	4	2	2	..	3	2	..	1
Tonsillitis.....	5	2	2	1	2	1	..	1
Otitis media.....	3	1	2	..	3	1	2	..
Adenitis.....	2	2	2	2
Erysipelas.....	2	2	1	1
Typhoid fever.....	2	2	2	2
Neuritis.....	2	1	1	..	1	1
Measles.....	2	2	1	1
Purpuric arthritis.....	1	1	1	1
Erythema.....	1	1	1	1
Infectious conditions not accompanied by exacerbations								
Urethritis (gonococci).....	4	1	2	1
Asthma.....	1	..	1
Influenza.....	1	..	1
Varicella.....	1	1
Abscess.....	2	2
Chancre.....	1	1
Pleurisy with effusion.....	1	1
Pericarditis.....	2	1	..	1
Total.....(23)	126	56	48	22	42	24	11	7

* This table illustrates which infections were associated with exacerbations of nephritis. Respiratory infections comprised the majority—ninety-five, or 72 per cent. Cultures were taken in most instances from the pharynx. Of the forty-two infections associated with exacerbations, 55 per cent were due to the streptococcus, as compared with 30 per cent of the eighty-four infections not inducing exacerbations.

group and 19 per cent of those in the latent group not accompanied by exacerbations showed this organism. This difference in the incidence of the streptococcus in these two groups of infections, with respect to the presence or absence of exacerbations, is sufficiently great to be of significance. In the progressive and fatal group, on the contrary, the streptococcus persisted, irrespective of whether or not acute infections were followed by exacerbations, which indicates that the patients were chronic carriers of the organism.

Of the exacerbations not accompanied by active infection, six occurred during convalescence, four during the latent and eleven in the progressive stage of the disease. It is of interest that the incidence of the streptococcus was considerably lower in these exacerbations than in those accompanied by active infections.

It also may be noted in table 8 that the relative number of infections in each group of cases was approximately equal, but that exacerbations of nephritis associated with infection were more frequent in the latent and progressive groups. In the well group, 25 of the 37 infections were contracted after complete recovery from nephritis was established, and it is important to observe that in only one case (7) on two occa-

TABLE 8.—*Correlation of the Total Number of Infections Noted in Each of the Three Groups of Cases with the Frequency of Str. Haemolyticus and of Exacerbations*

	Well Group (22 Cases)	Latent Group (20 Cases)	Progressive or Fatal Group (36 Cases)
Infections			
Total number.....	37	30	55
Number associated with exacerbations.....	9 (24%)	14 (45.6%)	19 (33%)
Number not associated with exacerbations...	28 (76%)	16 (53.7%)	36 (67%)
Results of cultures from Str. haemolyticus			
Infections associated with exacerbations			
Positive.....	6 (67%)	7 (50%)	11 (52%)
Negative.....	2 (22%)	3 (21%)	6 (37%)
No culture.....	1 (11%)	4 (29%)	2 (10%)
Infections not associated with exacerbations			
Positive.....	9 (32%)	3 (19%)	19 (37.5%)
Negative.....	15 (54%)	8 (50%)	15 (37.5%)
No culture.....	4 (14%)	5 (31%)	5 (25%)

sions were significant abnormalities found in the urine; twenty-three infections (five of which were due to Str. haemolyticus) had no apparent adverse effect so far as nephritis was concerned. It is obvious, then, that infections arising during the convalescent stage do not necessarily prevent recovery, and after recovery has been established, do not cause relapses of nephritis; on the other hand, exacerbations are more frequently associated with streptococcic infections in the latent and progressive stages. This suggests that patients who are destined to recover from nephritis become refractory or immune to infections during the convalescent stage and remain so after recovery has occurred; whereas in the latent and progressive stages this is not true, for the patient then appears to be more sensitive to streptococcic infections.

Further analysis of the progressive group shows that many patients with the chronic form of hemorrhagic nephritis presented recurring or chronic streptococcic infection (cases 56, 60, 63, 50, 51, 52, 68, 70 and 75), while an equal number showed only the streptococcus, and infections were insignificant (cases 49, 53, 56, 50 62, 64, 66, 69 and 71);

in a smaller number, infection occurred, but the streptococcus was not found (cases 57, 58, 73, 76 and 78); only four patients failed at any time to show either infection or the streptococcus (cases 54, 61, 72 and 74). With the exception of the few patients in whom the streptococcus was never obtained, the presence and persistence of this organism were characteristic of this stage of the disease, even though manifestations of infection were absent. Whether the mere presence of the streptococcus in the pharynx of patients in whom infections were not demonstrable is of significance in causing a continuation of the nephritis and can be interpreted as an actual chronic infection cannot be answered at present. It should be emphasized, however, that recurring active streptococcic infections or the "carrier state" (a total of 66 per cent of patients with progressive nephritis in contrast to 15 per cent of persons in the general population) and the absence of acute active infection at the onset are the chief characteristics of this chronic type of nephritis. Furthermore, the absence of demonstrable infection does not necessarily mean that infection is not present. Occult infection may exist, particularly in the accessory nasal sinuses, and may be important in this type of the disease, as in case 69, which showed chronic infection of the ethmoid cells, discovered only at postmortem examination.

EFFECT OF OPERATIVE PROCEDURES ON THE INCIDENCE OF: RECURRING INFECTIONS, STR. HAEMOLYTICUS, EXACERBATIONS OF NEPHRITIS, THE NATURAL HISTORY OF NEPHRITIS

If infection initiates hemorrhagic nephritis, the logical procedure which might conceivably exert a beneficent influence on the progress of the disease seems to be the removal of the infected tissue or tissues. Such an opinion was held by Longcope⁴ and Platt,²⁶ and vigorous effort to this end has been made. The object theoretically to be attained by such procedures is the elimination of the infected tissues and the infecting organism.

Operative procedures were performed with the close cooperation of Dr. Crowe and his staff in forty-nine cases in this series: forty-three were tonsillectomies and adenoidectomies, of which four were combined with antrectomy; two were dental extractions, and four were operations on the accessory nasal sinuses only. Unfortunately, there were only sixteen cases in which infections were presented for which operative procedures might have been performed but for several reasons were not. Although realizing that this number is too small to serve as an adequate control group, we have, nevertheless, presented the group as a basis for comparison with the operative cases. The data covering the time of operation (month of disease), the number of patients exhibiting postoperative infections and exacerbations of nephritis and the pre-

operative and postoperative incidence of the hemolytic streptococcus in both groups are summarized in table 9.

This table shows that elimination of foci of infection apparently did not prevent either postoperative infections or exacerbations of nephritis, since the average number of each was greater in the operative than in the nonoperative cases. Furthermore, operation did not appear to influence the incidence of the streptococcus in the nasopharynx; there was an apparent postoperative decrease in the well and latent groups, but there was also a parallel reduction in the patients of these two groups who were not operated on; in fact, six of the seven well

TABLE 9.—*Effect of Operative Procedures on the Incidence of Postoperative Infections, Exacerbations and Str. Haemolyticus*

Stage of Nephritis	Group Operated On								
	Cases	Time of Operation, Postoperative of Infection	Cases Nephritis	Infections per Case, Average	Cases with Exacerbations	Exacerbations per Case, Average	Str. Haemolyticus		
							Pre-operative	Tissue from Operation	Post-operative
Well.....	14	2.4	10	2.6	5	1.8	13	10	6
Latent.....	16	2.6	8	2	3	1.6	13	9	5
Progressive or fatal.....	19	12.3	11	3.2	7	1.5	13	8	14

Stage of Nephritis	Group Not Operated On							
	Cases	Cases with Infection after Active Stage of Nephritis	Infections per Case, Average	Cases with Exacerbations after Active Stage	Exacerbations per Case, Average	Str. Haemolyticus		
						Active Stage	Well, Latent and Progressive Stages	
Well.....	7	3	1	0	0	6	1	
Latent.....	5	4	1.5	1	—	4	2	
Progressive or fatal.....	4	4	1.2	1	—	2	3	

patients who were not operated on eventually showed negative cultures. Because of the inadequate number of controls (patients who were not operated on) one might accept the decreased incidence of the streptococcus in the well and latent groups as related to the operative procedures; if so, then a parallel diminution should be expected in the progressive and fatal group, but table 9 reveals that the incidence remained unchanged, irrespective of whether or not operation was done. The decrease of this organism in the former two groups and its persistence in the latter group, we believe, are related more nearly to the resistance of the patients to the infecting organism than to the operative procedures.

Since a larger number of the cases in the progressive and fatal group came under observation at later stages than the cases in the other two groups, it is possible that a delay in instituting surgical measures might explain the persistence of the streptococcus, and perhaps, indirectly, the progressive nature of the disease in these cases. Operation in this

group was performed usually during the twelfth month of the disease, or approximately ten months later than in the well and latent groups. The four progressive cases in the control group were too small a number to refute this point. Of the nineteen progressive cases in the other group, however, operation was performed in six during the second and third month, and in four during or before the sixth month of the disease. The possibility, therefore, that delay in operation was responsible for the persistence of the hemolytic streptococcus and the progression of nephritis seems unlikely. The patients in the series of cases reported recently by Platt²⁶ (1932) were apparently benefited by operation, but he presented no control cases, and no differentiation was made between the effect of operation in cases in which there was eventual recovery, in those which remained latent or in those which became progressive. Moreover, the course of the disease in individual cases, as described by him, differed in no manner from the progress of the disease in cases of our nonoperative group. Although it is possible that acute recurrences of a streptococcic infection and of nephritis may be prevented by operative procedures, such as tonsillectomy, it appears that factors other than the operative attempt to eliminate foci of infection must account for recovery or progression in nephritis.

COMMENT

The view that streptococcic infections cause hemorrhagic nephritis is given strong support by the evidence presented in the analysis of this series of cases. These infections, as in other series, are confined almost entirely to the respiratory tract. It is true, however, that a small number of patients, four, all with the progressive type of the disease, failed to show active infection at any time during its course, although four of the five carried the streptococcus in their respiratory passages. However, it will be of interest eventually to determine, if possible, the significance and importance of the mere presence of the streptococcus in relation to both the cause and the progress of nephritis; for it is not improbable that the "carrier state" is a condition sufficient in itself to incite the disease without producing objective evidence of infection.

The bacteriologic data are confined, however, to the incidence of *Str. haemolyticus*. That other organisms, such as the typhoid bacillus or the pneumococcus, cause nephritis is not denied, but we found no evidence in this series, with the possible exception of case 33, to support this view. With the exception of the cases of pulmonary infections,

26. Platt, Robert: The Effect of Removal of Septic Foci on the Course of Nephritis, *Quart. J. Med.* 1:499, 1932.

detailed identification of bacteria other than the streptococcus was not carried out, and it is possible that other organisms may eventually be found to explain both the cause of nephritis and the inability to demonstrate the streptococcus in the eleven cases in which this organism was not found.

In addition to the bacteriologic aspects of the infections associated with acute hemorrhagic nephritis, further interesting relationships between infection and this disease were developed in this study. Hitherto, attempts to explain the influences, favorable or unfavorable, on the course of nephritis have concerned themselves with four factors: (1) the recurrence or persistence of the causative infection, (2) the persistence of the streptococcus, (3) the elimination of foci of infection and (4) the age of the patient. On the basis of this analysis, we suggest a fifth factor, namely, the character of the infection at the onset of nephritis. The analysis in the section dealing with the character of the infection at the onset of nephritis (p. 304) revealed that patients in whom nephritis developed after an acute infection accompanied by definite constitutional symptoms usually recovered, or their nephritis entered the latent stage; whereas in patients with nephritis associated at the onset with chronic infection the disease usually became progressive.

The first and second factors were discussed and emphasized by both Addis²³ and Longcope.⁴ It was shown, however, that recurring infections, in spite of their relation to exacerbations, do not necessarily determine the ultimate outcome of the disease, for partial recovery to the latent stage or complete recovery from nephritis was not prevented by such infections, and whereas the progressive group was characterized by recurring infections in some cases, in others this factor was not obvious, and in a few patients active infection was never demonstrated. The presence of *Str. haemolyticus* in the respiratory tract does, however, vary with the stage of the disease, for it diminishes with recovery but persists during the progressive phase. It has been suggested that perhaps the mere presence of this organism may be sufficient to explain the progressive nature of nephritis, even though active infection is absent. We feel, however, that the variation in the incidence of the streptococcus during the course of the disease may be only one manifestation or result of some basic factor associated with the reaction of the patient to infection. The attempt to eliminate foci of infection by operative procedures is not always successful in the prevention of subsequent infection or exacerbations of nephritis, in influencing the frequency with which the streptococcus is found in the respiratory tract or in determining, eventually, recovery from or progression of the disease. It has long been recognized that hemorrhagic

nephritis in children, as recently reviewed by Guild,²⁷ very rarely progresses to the chronic stage. No difference, however, in the average age of our three groups of patients, as given in table 10, was found. It is interesting to note with respect to this question that in Guild's series of thirty-four carefully studied cases definite acute infection preceded the onset of nephritis in thirty cases, and chronic infection in only four cases. By analogy, one is inclined to suggest that the outcome of nephritis in children is related to the character of the causative infection, as well as to the age of the patient.

It has seemed to us that the presence or absence of active infection at the onset of nephritis is of greater significance in explaining eventual progress of the disease than the other four factors combined. If this assumption is true, it is suggested that patients in whom both local and constitutional manifestations of acute infection develop possess the

TABLE 10.—*Decades of Life of Seventy-Seven Patients with Hemorrhagic Nephritis**

Age, Years	Well	Nephritis Latent	Nephritis Progressive or Fatal
1-10.....	1	..	1
10-20.....	6	4	9
20-30.....	11	8	16
30-40.....	4	7	8
40-50.....	..	1	1
Average age.....	22	23	25

* The frequency of nephritis increased with age through the third decade, then decreased. There was a relatively equal distribution of well patients, patients with latent nephritis and patients with progressive or fatal nephritis in each decade. Age, therefore, in this series, was not a primary factor in the prognosis of nephritis.

capacity to react to the infecting organism, and owing to or as a result of this reaction, a resistance to the infection is acquired; thereafter, recurring infections are usually without influence, so far as the nephritis is concerned, recovery from the disease ensues, and simultaneously the streptococcus disappears. Excellent examples among the nineteen of twenty-one well cases, and nineteen of twenty latent cases, which illustrate this point are cases 2, 15, 21 and 23. In progressive nephritis, on the other hand, the capacity to react to the infecting organism is lacking. Both local and constitutional manifestations of active infection are therefore slight, a state of immunity to the streptococcus does not develop, and consequently either recurring streptococcic infection or merely the "carrier state" persists as a manifestation of the chronic stage of the disease. Typical among the twenty cases of progressive nephritis illustrative of this are cases 49, 57, 65 and 71.

27. Guild, H. G.: *The Prognosis of Acute Glomerular Nephritis in Children*, Bull. Johns Hopkins Hosp. 48:193, 1931.

Recovery from nephritis depends, therefore, according to the foregoing suggestion, largely on the capacity of the patient to react favorably to infection. This may account for the favorable outcome in children. Although operative procedures may hasten the cure of infection and the elimination of the infecting organism in some cases, the ultimate favorable result depends on the capacity of the patient to establish some form of resistance to infection by the hemolytic streptococcus. Disappearance of the streptococcus in cases that go on to recovery and in cases which become latent, and persistence of the organism in the progressive stage of the disease, might, therefore, be manifestations of the presence or absence of resistance to infection.

SUMMARY AND CONCLUSIONS

An analysis of the relationship between infection with *Str. haemolyticus* and hemorrhagic nephritis in a series of seventy-eight cases observed for from one to eight years is reported. Twenty-two of the patients are well, twenty-one are in the latent stage of the disease, seventeen are in the progressive stage and nineteen are dead.

Infections, usually of the upper respiratory tract, caused by *Str. haemolyticus* (alpha type, in a few cases), preceded the onset of hemorrhagic nephritis in the great majority of cases in this series.

Pneumococcic pneumonia, rheumatic fever and syphilis were not considered as a cause of hemorrhagic nephritis in this series.

Str. haemolyticus is apparently related to the progress of nephritis; for the numbers in which it occurred diminished markedly during recovery but persisted during the progressive stages of the disease. In eleven cases, however, hemolytic streptococci were not shown at any time during the course of the disease.

The cases of hemorrhagic nephritis which were preceded by acute infection manifested by both local and constitutional reactions almost always ended in recovery or entered the latent phase; the cases of nephritis associated with chronic infection at the onset almost always became progressive.

The prodromal period between the beginning of infection and the onset of nephritis varied from three to twenty-eight days; the most frequent interval was seven and the average was ten and nine-tenths days.

A seasonal variation in the onset of hemorrhagic nephritis coincided with months during which respiratory infections are most frequent in Baltimore.

Exacerbations of nephritis in most instances followed streptococcic infections of the upper respiratory tract; these exacerbations occurred more frequently in the latent and in the progressive stages of the disease. The prodromal period between infection and the exacerbation

of the nephritis was usually from twenty-four to forty-eight hours, in contrast to the prodromal period at the onset of nephritis. Exacerbations also occurred without relation to infection, and also after operative procedures.

Streptococcic infections which occurred during the convalescent stage did not prevent recovery from nephritis; and after recovery was established they rarely caused relapses; whereas the "carrier state," with or without recurring evidences of active infection, was characteristic of the progressive stage of hemorrhagic nephritis.

Surgical removal of foci of infection may fail to influence the outcome of hemorrhagic nephritis.

It is suggested that recovery from or progression in hemorrhagic nephritis is related more to the character of the causal infection; a severe acute infection presages a favorable course; a chronic infection, an unfavorable outcome. It is also suggested that patients with acute infection possess the capacity to react to *Str. haemolyticus*, so that some form of resistance to the infection develops, and as a result recovery from nephritis follows and disappearance of the organism occurs. In patients with chronic infection, this capacity to react to streptococcic infection is lacking, a resistant state does not develop, and as a result the organism persists and the nephritis becomes chronic.

Dr. Warfield T. Longcope permitted us to analyze his carefully studied series of cases of hemorrhagic nephritis and also gave many suggestions and helpful criticisms in the preparation of the manuscript.

THE VISCEROGALVANIC REACTION

E. A. SPIEGEL, M.D.

AND

M. G. WOHL, M.D.

PHILADELPHIA

The differential diagnosis of visceral diseases is often aided by a study of the associated referred pain of the hyperalgetic zones of the skin and the tender areas of the muscles. Such a study, however, fails in many cases because the subjective complaints of the patients may be unreliable. It is desirable in such cases to localize pain by objective methods. It is known from the work of Head¹ and of MacKenzie² that diseases of visceral organs produce many reflexes in the skin, such as viscerovasomotor and visceropilomotor reflexes. There are also segmental reflexes from the viscera which cause localized hypertonicity of certain muscles, the so-called visceromotor reflexes. These phenomena are of clinical importance; however, they are not always found. A more delicate objective method for the demonstration of referred pain in cases of visceral disease seems therefore to be desirable.

In such cases the segments of the spinal cord corresponding to the organ involved are in a state of hyperexcitation. This hyperexcitation involves both the somatic and the vegetative segmental centers, as shown by the hyperalgetic zones and the aforementioned reflexes. Consequently, increased nerve impulses are carried not only along the motor nerves but also along centrifugal vegetative nerves to different vegetative organs, e. g., in the skin. Excitation of the vegetative centers induces an increase of the electric potentials of the skin, as shown in psychic excitation, viz., by emotion (Tarchanoff's³ phenomenon), or in artificial stimulation of the various parts of the central nervous system (Langworthy and Richter⁴ and others). It seemed, therefore, probable that the increased excitation of the segmental centers associated with referred

The expenses of this study were partly defrayed by a grant from the Ella Sachs-Plotz Foundation.

From the Department of Experimental Neurology, D. J. McCarthy Foundation and Department of Medicine, Temple University Medical School.

1. Head, H.: *Brain* **16**:1, 1893; **17**:339, 1894; **19**:153, 1896. Head, H., et al.: *Studies in Neurology*, New York, Oxford University Press, 1920.

2. MacKenzie, J.: *Symptoms and Their Interpretation*, London, Shaw & Sons, 1920.

3. Tarchanoff: *Arch. f. d. ges. Physiol.* **46**:46, 1890.

4. Langworthy, O. R., and Richter, C. P.: *Brain* **53**:178, 1930.

pain becomes manifest by an increase of the electric potentials in the corresponding dermatomes. Such a reaction was indeed found and was called viscerogalvanic reaction in a preliminary report made by us.⁵ A more detailed account of this phenomenon is given in the present paper.

METHOD

The electric potential of the skin is measured by the so-called compensation method, i. e., by opposing to this potential a known variable potential. As long as one electromotive potential is stronger than the other a current will flow which may be indicated by a sensitive galvanometer. When the known variable potential is as strong as the potential of the skin, the galvanometer will show no deflection. A Leeds and Northrup portable galvanometer or a Sanborn string galvanometer was used. A control box with a neutralizer similar to those used in making electrocardiograms provided the variable potential. This neutralizer was standardized so that the number of millivolts furnished by it at each position of its knob was known.

The area of the skin to be studied was first connected with the galvanometer, and thus a deflection occurred. The neutralizer was then rotated until the galvanometer was brought to the zero point. This position of the neutralizer indicated the strength of the electric potential of the skin. Two nonpolarizable electrodes were used. They consisted of silver plates 2.5 by 4 cm. which were coated with silver chloride. Between the electrodes and the skin, gauze soaked in normal potassium chloride was employed, as recommended by Keller.⁶ In a few cases a 10 per cent solution of sodium chloride was used. One electrode was fastened by bandage under constant pressure to the ventral side of one forearm of the patient or to the forehead^{6a} and the other (testing) electrode was applied to various sites to be studied. It is extremely important to apply the latter electrode on the skin with as little pressure as possible. The metal electrode was therefore provided with an insulated handle; one half of the gauze was fixed on the metal plate by rubber rings and the other half hung freely down. The latter half of the gauze was laid on the skin, while the metal electrode was held in such a way that only its edge touched the skin.

It is important to have the patient completely relaxed so as to avoid errors due to muscular contractions; furthermore, the patient should be in a warm room to avoid reflexes of the skin from cold air, and the bed on which the patient lies should be insulated with glass cups. The electrodes are to be applied to each area for approximately the same length of time, since the potentials are usually lowered by longer or by repeated application of the electrodes. Very hairy patients have to be shaved several days before the examination.

The sensation of the skin was tested, as a rule, after the record of the potentials was taken. Thus, these records were not influenced by mechanical irritation of the skin due to the examination for sensation nor by previous knowledge of eventual hyperalgetic zones.

5. Spiegel, E. A., and Wohl, M. G.: *Klin. Wchnschr.* **11**:1272, 1932.

6. Keller, P.: *Arch. f. Dermat. u. Syph.* **162**:582, 1930.

6a. The uniform pressure maintains the potential on this site at a low figure. This is far more desirable for the patient than to destroy the epidermis as recommended by Keller in order to bring the potential of the skin to zero.

Thirty-two patients with abdominal or thoracic pain were examined, and fifteen without visceral disease were used as controls. Among the first group there were eight patients with angina pectoris, ten with gastric or duodenal ulcer, one with spastic colitis, one with chronic appendicitis, four with subacute cholecystitis, seven with nephrolithiasis and one with pulmonary tuberculosis.

TABLE 1.—*Measurements of the Potentials of the Skin on Fifteen Controls*

Name	Sex*	Disease	Skin Potentials, Millivolts						Comment
			Left			Right			
			Face	Trunk Min.-Max.	Lower Extremity (Thigh)	Face	Trunk Min.-Max.	Lower Extremity (Thigh)	
B. L.	♀	Adiposity.....	9	1-18	7	14	1-13	1	
C. V.	♀	Diabetes mellitus	21	6-13	6	21	7-23	3	
D. A.	♀	Neurosis.....	32	17	27	35	16	23	
E. B.	♀	Hyperthyroidism	8	3-14	17	19	6-10	10-13	
E. P.	♀	Hysteria.....	9	2-19	12	13	3-19	13	Determination made 1/26/32
			9	7-18	6	13	12-15	17	Determination made 2/9/32
G. L.	♀	Hypothyroidism	4	3-14	6	7	1-14	5	
G. R.	♀	Adiposity.....	17	12-31	20	22	12-31	22	Desiccated thy- roid 3 grains daily for 1 week; maxi- mum around umbilicus
H. R.	♀	Epilepsy.....	12 mamma, 24	8-10	0	14 mamma, 29	5-7	0	
L. A.	♂	Enuresis noc- turna; masto- dynia (left side)	10	7-14	4	5	6-14	5	Mamma, left side, 18; mamma, right side, 6
M. K.	♂	Myxedema.....	31	10-13	8	29	4-9	7	Determination made 3/1/32
			14	5-11	14	15	7-13	9	Determination made 3/5/32
M. S.	♀	Hypothyroidism (postoperative)	35	5-23	12	33	14-22	11	Under thyroid medication; determination made 2/9/32
			18	10-13	5	14	12-13	11	Determination made 3/5/32
P. H.	♀	Dysmenorrhea...	25	11-21 (subclavicular)	13	31	12-14	13	Rouge on face
S. G.	♂	Hypothyroidism	20	23	26	18	14	31	Without thy- roid medica- tion for 3 weeks
S. V.	♂	Neurosis.....	19	5-16	17	15	5-21	15	Maximum around nipple
M. G.	♂	Normal.....	0	3-13	..	0	3-4		

* ♀ indicates female and ♂, male.

RESULTS AND COMMENT

The measurements of the potentials of the skin of our fifteen control patients without painful visceral disease are summarized in table 1.

The measurements show considerable differences in different areas of the body, even in a normal person, as already pointed out by Munk

TABLE 2.—*Potentioelectric Measurements of the Skin in Visceral Diseases with Referred Pain**

Case	Name	Sex	Date	Diagnosis	Hyperalgetic Zone	Skin Potentials, Millivolts		Comment
						Left	Right	
1	B.	♂	1/29/32	Spastic colitis	d8-d12 (maximum, upper portion of left side of abdomen)	d4-6 : 4.17 d8 : 25 d9 : 34(+17) d12 : 29 L2 : 13 L2 : 15	d4-6 : 10 d9 : 30(+20) d12 : 29 L2 : 13	
2	B. F.	♂	4/23/32	Duodenal ulcer	No	e4-d6 : 10.23 d8-9 : 27 d10-12 : 32(+4) L2 : 16	e4-d6 : 20.22 d8-9 : 29 d10-12 : 31(+9) Right leg amputated	
3	C. A.	♀	2/23/32	Duodenal ulcer	No cutaneous hyperalgesia; only pain on pressure in epigastrium	V-d4 : 23.25 d8-9 : 11 d10-12 : 15 L2 : 20	V-d4 : 17.19 d8-9 : 34(+15) d10-12 : 30 L2 : 13	
4	C. J.	♂	5/ 9/32	Cholecystitis	d8 (right > left)	V : 9 e7 : 19 d2-d9 : 3.8 d11-12 : 22	V : 5 e7 : 23 d4 : 19(mamma) d2-7 : 4.8 d9 : 11 d11-12 : 20	
5	D. W.	♂	2/ 6/34	Nephrolithiasis	Anterior surface: d12-L2 (left) d12-L1 (right) (left > right) Posterior surface: d10-12 (slight; left > right)	V-d8 : 0.23 d10 : 40(+17) d12-L2 : 38	V-d10 : 10.28 d12 : 47(+19) L2 : 33	
6	F. R.	♂	11/ 7/33	Cholelithiasis; apical tuberculosis	d9-10 (slight) e4 (both sides)	e4-d9 : 0.7 d10-12 : 20(+13) d12-L1 : 15 s2 : 16.5 Face : 4.8 e4 : 23 d4-6 : 16 d9-10 : 18 d11-L2 : 4.8	e4-d9 : 0.7 d10-12 : 11 d12-L1 : 5 s2 : 15 V-L2 : 0.7 Only e4: 19(+12)	
7	F. B.	♂	4/ 5/32	Gastric ulcer	Very slight hyperesthesia in the epigastrium (d6-7)	d2-7 : 23 d8-9 : 35(+12) d11-12 : 26 L2 : 14	d2-7 : 29 d8-9 : 23 d11-12 : 27 L2 : 18	

S	G. S.	♂	11/18/32	Functional hyper-acidity; chronic appendicitis	Very slight, d10	Maximum d9-10	Accurate figures of potentials unobtainable
9	M. W.	♀	4/22/32	Gastric ulcer	No	V : 27 d2-6 : 12-14 d9 : 7 d12 : 21	V : 21 d2-6 : 21 d9 : 14 d12 : 12
10	G. A.	♀	2/ 1/33	Cholecystitis	Anterior surface: d8-9	V-d7 : 1-4 d9-10 : 9(+5) d10-12 : 8 L2 : 3	V-L2 : 1-5 d10-12 : 7(+2) 10% sodium chloride
11 (fig. 1)	L. M.	♂	3/30/32	Duodenal ulcer	Posterior surface: d8-10 Slight hyperesthesia; d7-8 and d11 (right side)	c4-d6 : 9-11 d8 : 13 d11 : 12.5 d12 : 9 V : 13 d2-10 : 0 d12 : 7 L2 : 25	c4-d8 : 3-9 d11 : 13.5 d12 : 12.5 V : 5 d2-4 : 0 d8 : 9 d11-12 : 36(+27) L2 : 26
12	M. J.	♂	4/13/32	d8 on the left side more marked than on the right	V : 14 d2-3 : 29 d8-9 : 35(+5) d11-12 : 32 L2 : 10	V : 26 d2-5 : 23-28 d8-9 : 21 d10-12 : 26 L2 : 3
13	M. B.	♀	1/25/33	Gastric ulcer	d6-7	V-d4 : 1 d7-12 : 3(+2) L1 : 1	V-d4 : 1-2 d7 : 3(+1) d9-12 : 1 L1 : 2
14	M. B.	♀	4/18/34	Pulmonary tuberculosis; duodenal ulcer	c4-d2 (left side) d6-8 (epigastrium, slight)	V : 7 d2 : 108(+49) d5 : 32 d8 : 39 d10-12 : 59	V : 32 d2 : 92(+8) d5 : 20 d8 : 2 d10-12 : 84
				Nephrolithiasis	d12-L1 (left, only on back)	Anterior surface: c4-d10 : 2-16 d12-L1 : 18 Posterior surface: c4-s2 : 0-13	c4-d10 : 9-20 d12-L1 : 24 c4-s2 : 3-7
						After examination of sensation: d6-d10 : 2-3 d12-L1 : 30	

* The following abbreviations are used: c, cervical segments of the skin; d, thoracic segments of the skin; L, lumbar segments of the skin; s, sacral segments of the skin, and V, face (area of the trigeminal nerve). The numbers in parenthesis indicate by how many millivolts the potentials of the hyperalgetic zone exceed those of the other parts of the trunk.

TABLE 2.—*Potentiometric Measurements of the Skin in Visceral Diseases with Referred Pain**—Continued

Case	Name	Sex	Date	Diagnosis	Hyperalgetie Zone	Skin Potentials, Millivolts		Comment
						Left	Right	
15	N. J.	♂	1/25/33	Nephrolithiasis	No cutaneous hyperesthesia; spontaneous pain in left groin	V : 9 c4-L2 : 1-5	V : 3 c4-L2 : 1-7	10% sodium chloride
16	P. G.	♂	4/24/34	Duodenal ulcer	d7-12 (right) d10-12 (left)	V-d2 : 0 d4 : 12 d7 : 15(+3) d8-10 : 9 d11-12 : 1 L2 : 12	V-d6 : 2-3 d7 : 9 d8-9 : 10 d9-10 : 16.5(+13) d11-12 : 12 L2 : 9	
17	P. M.	♀	2/20/34	Cholelithiasis	e4:d7-9 (right)	Anterior surface: V-L2 : 0-5 Posterior surface: c4-s2 : 13-20 Only d6-7: 28 d10 : 22	V-L2 : 0-2 Only c4: 7 c4-s2 : 2-13 d10 : 22	
18	R. R.	♀	5/12/34	Nephrolithiasis	Anterior surface: d11 (left) Posterior surface: d9-11 (left)	e2-L2 : 0-4 d10-12 : 0(+4) Rest of trunk : 0-2	e2-L1 : 0-4 c4-s2 : 0-3	
19	R. M.	♂	12/19/33	Nephrolithiasis; sigmoiditis	d12-L1 right > left	Anterior surface: c4-d9 : 7-13 d10-12 : 16 d12-L1 : 17(+4) L3 : 13 Posterior surface (median line): c4-d6 : 0-3 d8-9 : 16 d11-12 : 47(+31) V-d12 : 1-3 Only d7-8: 7 d8-9 : 14(+11)	c4-d11 : 0-3 (Only perium-bilical : 15) d12-L1 : 18(+3) L3 : 3 d12-L1 : 24(right) d12-L1 : 31(left) s2 : 12 V-d12 : 1-5 Only d7-9: 9(+4)	On the back measurement only in median line possible on account of intensive growth of hair
20	S. R.	♂	2/25/33	Duodenal ulcer	d8-10	V-d12 : 1-3 Only d7-8: 7 d8-9 : 14(+11)	V-d12 : 1-5 Only d7-9: 9(+4)	
21	S. A.	♂	2/25/33	Gastric ulcer	d8 (left) and e4 (only very slight hyperalgesia)	V-d12 : 4-5 Only c4-d2 : 12.5	V-d12 : 1-5 Only d9-10 : 7	

22	V. F.	♂	2/ 1/33	Gastric ulcer; inguinal hernia	d3-d12 (maximum d12, right > left)	V-e4 : 1 d6-10 : 5 d12 : 8 L2 : 5	V : 9 e4 : 7 d6 : 11 d8 : 9.5 d9-10 : 11.5 d12 : 14.5(+3) L2 : 11	10% sodium chloride
23	W. M.	♂	2/21/33	Nephrolithiasis (acute pain)	d12-L1 (bilateral)	V-L1 : 0.5-1	V-L1 : 1-3	10% sodium chloride
24	W. R.	♀	2/21/33	Nephrolithiasis 3 years ago	No	V-d12 : 0-7	V-d12 : 1-9	
25	L. M.	♂	3/22/32	Coronary pain	No hyperalgesia; only slight pain on left side of chest	V : 21 d2-6 : 8(+2) d8-12 : 6	V : 27 d2-6 : 11 d8-12 : 13	
26	L. W.	♂	3/24/32	Coronary thrombosis	Maximum: d2-d4 (left) d6-12 (slight, left)	V : 35 d2-6 : 40(+9) d8-L2 : 29-31	V : 28 d2-6 : 37(+4) d8-L2 : 24-33	
27	P. W.	♂	1/23/34	Coronary sclerosis	Uncertain (d3-4)	V : 12 e4 : 16 d4 : 10 d8 : 21(+14) d10 : 7 d12 : 2 L2 : 7	V : 12 e4 : 4 d4 : 0 d8 : 4 d9-12 : 0-3 L2 : 11	Patient under morphine ($\frac{1}{4}$ grain [11 mg.] every 3 hours)
28 (fig. 2)	S. J.	♂	3/24/32	Angina pectoris	e8-d4 (left)	V : 24 d2-4 : 31(+22) d9-12 : 0-9 L2 : 17	V : 18 d2-4 : 32(+18) d9-12 : 7-14 L2 : 13	
29	S. A.	♂	4/25/34	Coronary thrombosis	No	d8 : 16.5(+3) Other parts of trunk : 5-13	d2-4 : 20(+13) Other parts of trunk : 0-7	
30	S. O.	♀	4/25/34	Coronary thrombosis	d2-3 (slight, left)	e4 : 10 d2 : 27(+22) d4-5 : 18 d8-12 : 0-5	d4-5 : 18(+18) Other parts of trunk : 0-8	
31	Z. M.	♂	12/ 1/32	Coronary pain	d6-8 (left)	V : 2 e4 : 23 d4 : 49(+34) d6 : 37 d10 : 11 d12 : 15	V-d12 : 2-8	
32	Z. T.	♂	2/23/34	Coronary sclerosis	e4-d4 (left) e4-d2 (right)	e4 : 7 Face and rest of trunk : 0-3	e4 : 9 Face and rest of trunk : 0-5	

and Flockenhaus⁷ and by Keller⁶ in their studies of these potentials in conditions other than those investigated by us. We are here interested particularly in the potentials obtained on the trunk, because pathologic changes of the potentials in visceral diseases are found in this region. The highest values obtained in the dermatomes of the trunk in our control subjects were, as a rule, below 30 millivolts. In one case only (no. 7) a value of 31 millivolts was obtained around the umbilicus. The patient, G. R., who was obese, received 3 grains (0.195 Gm.) of thyroid daily. We found in other studies that this substance may increase the potentials of the skin. On the face, values up to 35 millivolts were obtained; from the palms and the soles even higher potentials could be led off.

In cases of visceral pain, as already mentioned, the regions where pathologic vegetative innervation of the skin is to be expected are mainly localized on the trunk, so it is often sufficient to limit the comparison of the potentials to the dermatomes of the trunk only. We considered high values that were obtained on the face or on the limbs to be pathologic only when the neighboring dermatomes of the neck and trunk showed an increased value. In other words, a high potential of the face or limbs as well as of the trunk indicated an irritation of a continuous series of spinal segments. Munk mentioned, rightly, that even in normal persons the values are sometimes irregular around the nipple and high around the umbilicus. In cases of such irregularities it is advisable to make the measurements in more lateral parts of the body, e. g., in the anterior axillary line.

The potentiometric measurements of the skin for patients with visceral disease and referred pain are shown in table 2 and in figures 1 and 2.

Hyperalgetic zones were found in twenty-five of the thirty-two patients with visceral pain. A comparison of the potentials of the patients with referred pain with those of the control subjects shows that the potentials of the hyperalgetic zones for ten patients exceeded 30 millivolts (figs. 1 and 2), the maximum value normally found for the dermatomes of the trunk. But even if the potentials led off from the hyperalgetic areas remain below 30 millivolts, the abnormal excitation of the vegetative elements in these dermatomes can be revealed if the potentials are compared with those of the remaining parts of the trunk. While three of the twenty-five patients showed no abnormal potentials, for thirteen cases the potentials of the hyperalgetic zones exceeded the maximal potentials on the other parts of the trunk by more than 10 millivolts (for five of the thirteen patients by from 20 to 30 millivolts

7. Munk, F. M., and Flockenhaus, M.: *Ztschr. f. d. ges. exper. Med.* **61**:363, 1928.

and for three by more than 30 millivolts). The potentials of the hyperalgetic zones for the remaining nine patients exceeded those of the other dermatomes of the trunk by less than 10 millivolts. It seems advisable to consider the reactions in the latter group as doubtful with the exception of those obtained for such patients as L. W. (case 26) for whom higher maxima than those obtained for the control subjects (more than 30 millivolts) were led off from the dermatomes of the trunk. The increased potentials are sometimes demonstrable on both sides in the

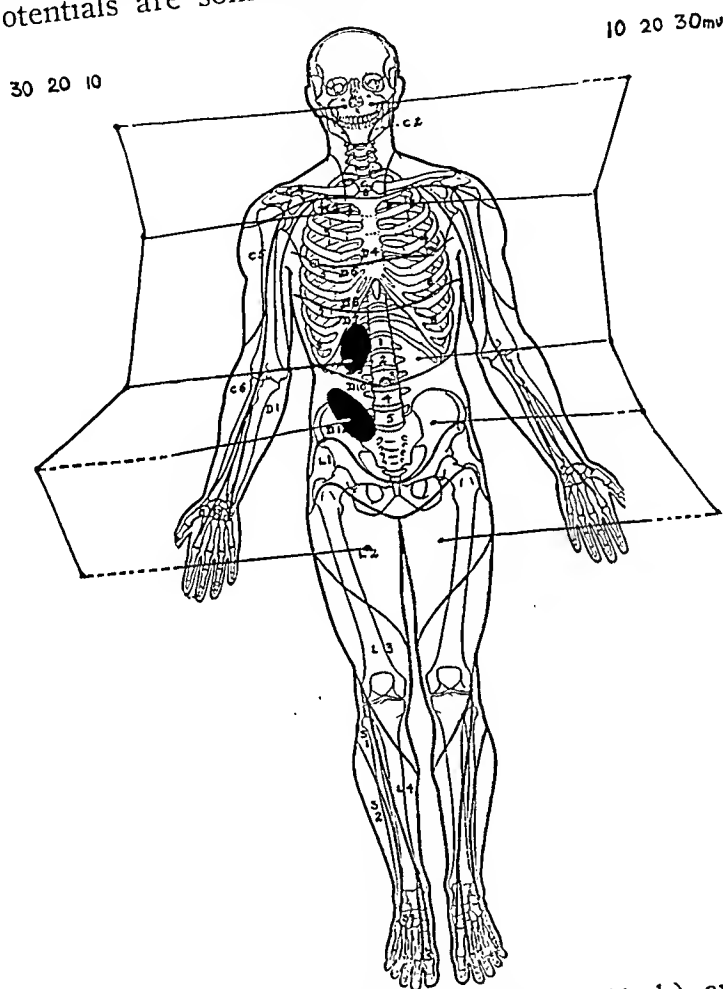


Fig. 1 (L. M., case 11).—Hyperalgetic zones (black) and potentials of the skin (in millivolts, represented by the abscissas of the graphs) in a case of duodenal ulcer.

respective segments, although the hyperalgesia is only unilateral (e. g., L. W., case 26; S. J., case 28 [fig. 2]).

Mechanical stimulation of the skin as used in examination of pain sensibility by pinprick can increase the potentials of the hyperalgetic zones (case 14, B. M.), while the potentials of the other dermatomes may remain low. As a rule, however, we studied the viscerogalvanic reaction before the examination of sensation. For two of the seven patients without cutaneous hyperalgesia, potentials were obtained on

the dermatomes corresponding to the diseased organs which exceeded those obtained on the rest of the trunk by more than 10 millivolts (C. A., case 3; S. A., case 29), and values above 30 millivolts were reached for B. F. (case 2) and C. A. (case 3). These observations show that the examination of the potentials in visceral diseases sometimes permits the localization of the corresponding segments, although the examination of the sensation fails to give such a localization. In this regard, case 27 is of special interest. The patient, P. W., was suffering

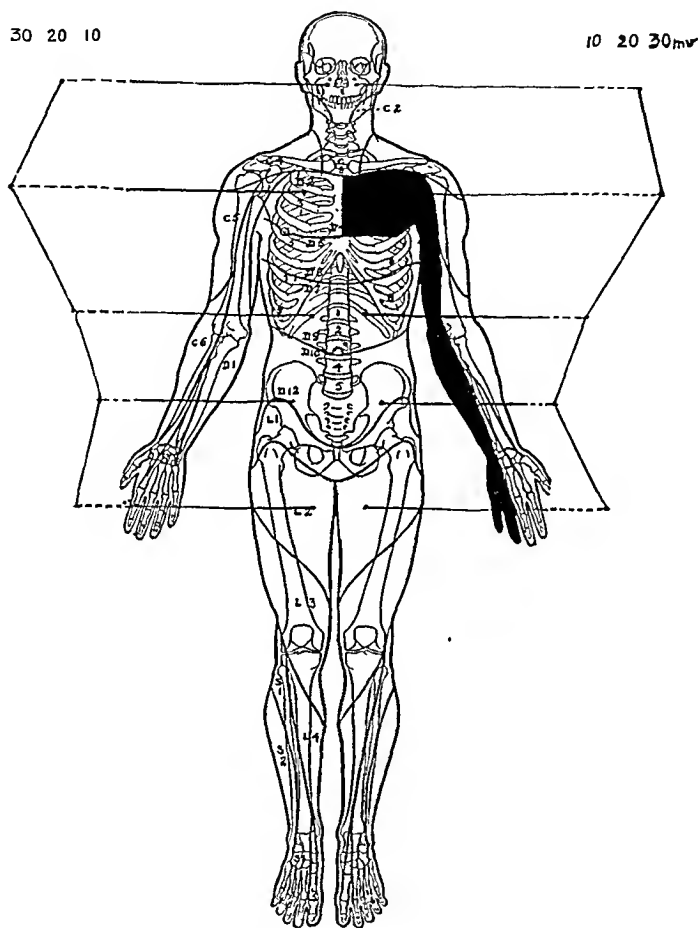


Fig. 2 (S. J., case 28).—Hyperalgetic zones (black) and potentials of the skin (in millivolts, represented by the abscissas of the graphs) in a case of angina pectoris.

from coronary thrombosis and was under the effect of morphine. He was therefore unable to localize the hyperalgesia; examination of the potentials, however, showed an increase in those of the left side of the chest. As morphine paralyzes the higher centers, where pain sensations enter consciousness, this observation indicates that the viscerogalvanic reaction can occur without the activity of these higher centers.

If one compares the area of hyperalgesia and the zone of increased potential, one may find in some cases that these two areas differ in their

extent and localization. This is to be expected if one considers the localization of the spinal centers of the sympathetic ganglions. It is known from the work of Gaskell,⁸ Langley⁹ and others that the pre-ganglionic fibers of the sympathetic chain leave the cord between the eighth cervical and the second or third lumbar segment. These fibers supply the entire body with vegetative impulses; the spinal centers of the vegetative elements of the skin of the body are limited, therefore, to segments between the eighth cervical and the second or third lumbar segment. It is apparent, then, that a certain segment of the cord supplies a much larger area of the skin with vegetative than with sensory fibers, as is shown in detail by the study of the pilomotor reflex (André Thomas¹⁰) and also of sweat secretion in diseases of the spinal cord (Foerster¹¹).

If such a segment is in a state of hyperirritation due to increased stimuli from a visceral organ, the zone of hyperalgesia is to be expected to be smaller than the zone of increased potential, i. e., the zone of increased vegetative innervation of the skin. Likewise the differences between the location of the hyperalgetic zone and the areas of increased potential can be easily understood. To illustrate: The first thoracic segment supplies the ulnar side of the arm with sensory fibers, but it sends vegetative impulses not only to the arm but also to the neck and the head; consequently, hyperirritation of this segment might result in an area of increased vegetative innervation including the face. Indeed reflex stimulation of the cervical sympathetic nerve was observed in some cases of angina pectoris by Gibson,¹² Bittorf,¹³ Conzen,¹⁴ and Misch and Lechner.¹⁵ This is in agreement with our observations on one of the patients (L. W., case 26) with angina pectoris, in whom the zone of high potential extended from the chest to the face, although the hyperalgesia was limited to the thoracic segments. In such cases of hyperirritation of the upper part of the thoracic segments the zone of increased vegetative innervation extends farther headward than the area of hyperalgesia. On the other hand, in cases of hyperirritation of the lower part of the thoracic segments or of the first two lumbar segments the zone of increased potential is to be expected to reach farther

8. Gaskell, W. H.: *J. Physiol.* **7**:1, 1886.

9. Langley, J. N.: *The Autonomic Nervous System*, Cambridge, England, W. Heffer & Sons, 1921.

10. Thomas, André: *Le réflexe pilomoteur*, Paris, Masson et Cie, 1921.

11. Foerster, O., cited by Guttman: *Ztschr. f. d. ges. Neurol. u. Psychiat.* **135**:1, 1931.

12. Gibson, G. A.: *Brain* **28**:57, 1905.

13. Bittorf, D.: *Arch. f. klin. Med.* **81**:65, 1904.

14. Conzen, F.: *Ueber die periphere Sympathicusaffection insbesondere ihre Aetiologie und Symptomatologie*, Leipzig, B. Georgi, 1904.

15. Misch, W., and Lechner, A.: *Klin. Wchnschr.* **8**:500, 1929.

caudally than the hyperalgetic zone. The first two lumbar segments of the cord, e. g., supply with vegetative fibers not only the corresponding dermatomes but also the skin from the tenth thoracic to the last sacral segment (Spiegel¹⁶).

In many cases hyperalgesia is found not in the whole extent of a dermatome but only in a relatively small part of it (fig. 1). Conceivably, in such a case only a part of the respective segment of the cord is in a state of hyperexcitation. It is easy to understand that under these circumstances only some of the vegetative elements of this segment are stimulated and that the zone of increased potential is also smaller than the area supplied from this segment with vegetative impulses. Thus, the viscerogalvanic reaction has a segmental distribution following the

TABLE 3.—*Potentials for L. W. (Case 26)*

Left	Skin Temperature, C.	Potential, Millivolts
Face.....	37.5	35
c4.....	35.9	..
d4.....	35.3	40
dS-9.....	35.3	29

TABLE 4.—*Potentials for L. M. (Case 11)*

Right	Skin Temperature, C.	Potential, Millivolts
d2-4.....	36.3	0
dS.....	36.5	9
d11-12.....	36.3	36

vegetative innervation of the skin by the respective segments of the spinal cord. The question arises as to which vegetative elements of the skin the viscerogalvanic reaction is to be attributed. Four groups of organs within the skin have to be considered: the vessels, the arrectores pili, the sweat glands and possibly the cells of the epidermis. In order to determine the eventual rôle of viscerovasomotor reflexes the temperature of the skin was measured in the various dermatomes in cases of referred pain in which the viscerogalvanic reaction was positive. It was found that different potentials may be led off from two areas that have the same temperature, e. g., the chest and the abdomen (tables 3 and 4).

This shows that the viscerogalvanic reaction does not depend on viscerovasomotor reflexes. Reflex contraction of the arrectores pili can also be excluded as a possible cause of the increased potentials, as the visceropilomotor reflex appears much more rarely than the viscerogalvanic reaction.

16. Spiegel, E. A.: *Die Zentren des autonomen Nervensystems*, Berlin, Julius Springer, 1928.

galvanic reaction; if the patient is examined, for instance in a warm room, the visceropilomotor reaction fails to appear despite a well developed viscerogalvanic reaction.

It may be inferred that the viscerogalvanic reaction is in relation to an increased activity of the sweat glands; this inference is strengthened by the fact that there exists also a close correspondence between the activity of the sweat glands and the galvanic response of the skin to psychic excitation (Darrow¹⁷). One can indeed find similarities in the two reactions. Both are more easily elicited with a warm skin; both show a decrease if the examination is repeated at short intervals. Ohm's resistance of the skin as measured with alternating currents is not changed in the galvanic response of the skin to sensory stimuli (Gildemeister¹⁸). We found, likewise, in the study of the viscerogalvanic reaction that the resistance of the skin measured with alternating currents may be the same in areas with quite different potentials (table 5). One should bear in mind, however, the possibility that nerve impulses

TABLE 5.—*Resistance of the Skin Measured by Alternating Current*

Area on Right Side	Resistance, Ohms	Potential, Millivolts
Face.....	3,600	26
c4.....	8,000	23
d4.....	6,500	23
d8-9.....	5,400	21
d11-12.....	5,700	26
L2.....	3,600	3

act not only on the sweat glands but also on the cells of the epidermis. This is applicable to the viscerogalvanic reaction as well as to the psychogalvanic reaction (Gildemeister¹⁸). To determine the eventual rôle of the epidermis in this phenomenon it will perforce be necessary to study the viscerogalvanic reaction in patients with congenital absence of sweat glands.

It should, however, be borne in mind that the galvanic skin response on psychic excitation (Tarchanoff's phenomenon) must be distinguished from the viscerogalvanic reaction; these two phenomena differ from each other mainly in two points: 1. While the Tarchanoff reaction usually affects the whole surface of the body and is normally due to stimulation of the higher and of the lower parts of the vegetative centers, the viscerogalvanic reaction shows a segmental distribution, indicating that mainly segments of the spinal cord are affected. 2. The Tarchanoff phenom-

17. Darrow, C. W.: *J. Exper. Psychol.* **10**:197, 1927.

18. Gildemeister, M., in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: *Handbuch der normalen und pathologischen Physiologie*, Berlin. Julius Springer, 1928, vol. 8, p. 765.

enon is a transitory reaction lasting a few seconds following a stimulus, while the viscerogalvanic phenomenon is a more or less continuous reaction, maintained by sustained impulses from the diseased internal organ.

SUMMARY

The electrical potentials of the skin as measured by the compensation method are often increased in areas which correspond to diseased visceral organs (viscerogalvanic reaction). This method can be employed as an objective means to demonstrate areas of referred pain.

EFFECT OF DIURETICS ON THE CARDIAC OUTPUT OF PATIENTS WITH CONGESTIVE HEART FAILURE

BEN FRIEDMAN, M.D.
NEW YORK

HARRY RESNIK JR., M.D.
NASHVILLE, TENN.

J. A. CALHOUN, M.D.
BOSTON

AND

T. R. HARRISON, M.D.
NASHVILLE, TENN.

Diuretic drugs are sometimes considered to be only of symptomatic value for persons with cardiac disease. Their beneficial effects in patients with pronounced dropsy are unquestioned, but minimal or latent edema is not generally considered as an important indication for their use.

Our own experience with diuretics has led us to believe that they possess much more therapeutic value than has been generally recognized. We have often observed amelioration of paroxysmal dyspnea, cough and other symptoms of cardiac failure, both in hospitalized and in ambulatory patients, following their use. This has occurred when no other change has been made in the therapeutic regimen and even when diuresis has been of slight degree.

We also gained the impression that the repeated use of diuretics in patients with minimal or latent edema tends to prolong life. With this in mind a group of case records were analyzed, and it was found that the patients who were treated vigorously with diuretics lived longer than nontreated patients with similar types of cardiac disease. However, since the patients were not rigidly controlled in regard to other therapeutic measures and since the number of cases was not sufficiently large to warrant statistical treatment, no definite conclusions could be drawn. Accordingly, we decided to make objective measurements of the effect of diuretics on circulatory and respiratory functions.

EFFECT OF THEOPHYLLINE ON VITAL CAPACITY

Observations were made on hospitalized patients who complained chiefly of dyspnea while at rest but who had either minimal pitting

From the Department of Medicine, Vanderbilt University School of Medicine.

edema or latent edema, as shown by loss of weight when diuretics were administered, without recognizable pitting. Their vital capacities were measured under standardized conditions before and after the administration of theophylline (chart 1). Ordinarily, patients who complain of dyspnea while at rest have slightly lower vital capacities in the evening than in the morning.¹ This tendency was noted in the subjects of the present study. However, on days when the patient received theophylline, the vital capacity was higher in the evening than in the morning in four of five comparisons. In eight of nine patients observed the level of the vital capacity seemed to be increased by the drug. The dif-

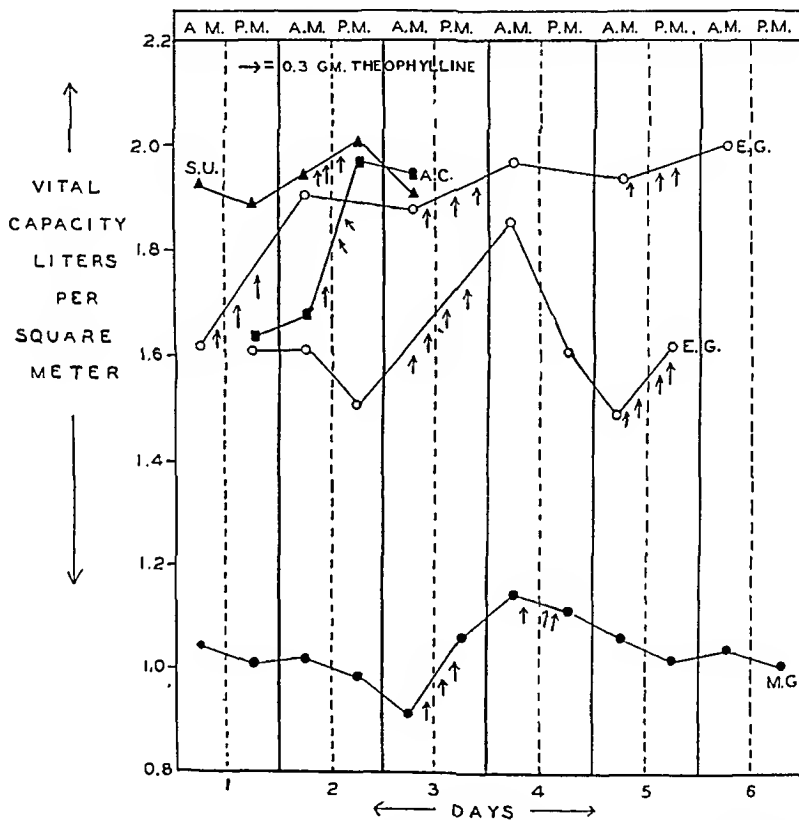


Chart 1.—Vital capacities of patients before and after the administration of theophylline.

ference was so slight as to be of questionable significance in several observations, but it was striking in others. In each of the patients

1. Harrison, W. G., Jr.; Calhoun, J. A.; Marsh, J. P., and Harrison, T. R.: (a) Studies in Congestive Heart Failure: XIX. Reflex Stimulation of Respiration as the Cause of Evening Dyspnea, *Arch. Int. Med.* **53**:724 (May) 1934; (b) The Cisternal Pressure in Congestive Heart Failure and Its Bearing on Orthopnea, *ibid.* **12**:1075, 1933; (c) Cerebrospinal Fluid Pressure and Venous Pressure in Cardiac Failure and the Effect of Spinal Drainage in the Treatment of Cardiac Decompensation, *ibid.* **53**:782, 1934.

whose vital capacities are recorded in chart 1, there occurred a slight diuresis, the body weight declining from $\frac{1}{2}$ to $2\frac{1}{2}$ pounds (from 0.25 to 1.1 Kg.) on the day theophylline was administered. Each patient was improved by the drug, although most of them complained of the nausea induced by it.

In presenting these results we deliberately have chosen patients who exhibited improvement in dyspnea with minimal diuresis. When patients are more edematous and striking diuresis occurs, there is frequently an associated amelioration of dyspnea of more marked degree.

The reason for the clinical improvement following minimal diuresis has been a subject of further study. Loss of pulmonary edema may be responsible in some cases but can scarcely be the sole factor, because relief of dyspnea may occur in persons who have no râles in the lungs. It is possible that decrease in spinal fluid pressure,^{1b} and diminution in volume of blood due to concentration of the blood may each play a rôle, but these possibilities have not been studied. Our attention has been centered rather on possible alterations in the state of the circulation as a result of diuretics.

EFFECT OF THEOPHYLLINE AND OF SALYRGAN ON THE CARDIAC OUTPUT AND RELATED FUNCTIONS

Measurements have been made of oxygen consumption (by analysis of the expired air), of arteriovenous oxygen difference (using the three sample acetylene technic) and of cardiac output, vital capacity, ventilation, body weight and heart rate before and after the administration of diuretics. All of the patients were hospitalized and studied while in the basal state. The details of the methods used have been presented in previous papers.² Since the method of measuring the cardiac output is difficult to apply to persons with severe congestive heart failure, most of the persons chosen for the study had only slight edema. They were all well accustomed to the procedures, and none of them displayed undue anxiety or apprehension.

The results are shown in table 1. Following the administration of a diuretic the patient lost 1 or more pounds of weight within twenty-four hours in eleven of twelve observations. In most instances the patient stated that the degree of dyspnea was diminished. Well marked increase in vital capacity occurred in five instances, slight increase in five, and no change in two. The quotient $\frac{\text{Ventilation}}{\text{Vital Capacity}}$ was diminished

2. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, *J. Clin. Investigation* **12**:751, 1933. Friedman, B.; Clark, G.; Resnik, Harry, Jr., and Harrison, T. R.: Effect of Digitalis on the Cardiac Output of Persons with Congestive Heart Failure. *Arch. Int. Med.*, to be published.

TABLE 1.—*Effect of Diuretics on the Circulatory and Respiratory Functions of Patients with Congestive Heart Failure*

Subject	Diagnosis	Date, 1933	Dyspnea*	Edema	Body Weight, Pounds	Ventilation		Heart Rate	Oxygen Consump- tion per Minute, per Cc.	Arterio- venous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Comment
						Vital Capacity, Liters	Vital Capacity					
G. S.	Hypertension; auricular fibrillation	8/ 8	+++	+++	212	1.50	7.40	..	366	96	3.81	Before treatment
		8/ 9	++	++	196	1.50	6.63	..	319	86	3.72	After 2 cc. of salyrgan
A. M.	Syphilitic aortic insuf- ficiency	8/25	++	+++	160	2.00	3.77	73	290	114	2.55	Before treatment
		8/26	+	++	150	2.90	3.71	81	278	118	2.36	After 2 cc. of salyrgan
		9/ 1	++	+	143	3.25	2.66	64	224	105	2.12	Before treatment
		9/ 2	+	0	136	3.30	2.62	68	232	132	1.76	After 2 cc. of salyrgan
A. T.	Mitral stenosis	7/29	++	++	95	1.75	5.60	..	185	100	1.85	Before treatment
		7/31	+	+	89	1.53	5.30	..	187	71	2.62	After 1.5 cc. of salyrgan
C. M.	Syphilitic aortic insuf- ficiency	8/ 3	++	+	133	2.10	5.92	56	201	73	2.74	Before treatment
		8/ 5	+	0	130	2.50	4.26	56	206	79	2.61	After 2 cc. of salyrgan
E. P.	Mitral stenosis; aortic fibrillation	5/ 3	+	+	124	1.08	3.68	52	193	76	2.55	Before treatment
		5/ 5	±	0	117	1.55	3.08	54	192	77	2.48	After 2 cc. of salyrgan
L. W.	Mitral stenosis; aortic fibrillation	11/3	+	+	125	2.95	1.74	52	161	77	2.10	Before treatment
		11/4	+	+	124	3.10	1.70	52	168	80	2.09	After 2 cc. of salyrgan
G. M.	Syphilitic myocarditis	9/18	+	±	132	2.20	4.64	72	225	91	2.48	Before treatment
		8/20	+	±	130	2.20	5.04	74	253	75	3.37	After 1.5 Gm. of theophyll- line daily for 2 days
L. M.	Hypertension	3/25	++	±	160	2.35	3.31	85	264	94	2.81	Before treatment
		3/27	++	±	159	2.50	3.06	98	262	95	2.76	After 1.5 Gm. of theophyll- line
L. W.	Mitral stenosis; aortic fibrillation	6/23	+	0	114	3.10	2.50	64	202	63	3.21	Before treatment
		6/30	0	0	116	3.55	2.46	84	213	68	3.13	After 0.9 Gm. of theophyll- line daily for 2 days
8/12			+	±	119	3.10	2.82	80	212	83	2.55	Before treatment
		8/15	0	±	118	3.40	2.49	76	217	75	2.90	After 0.9 Gm. of theophyll- line daily for 2 days
2/23			++	++	127	2.70	3.06	68	228	78	2.91	Before treatment
		9/ 1	+	+	122	3.00	1.98	68	210	70	3.01	After 0.9 Gm. of theophyll- line daily for 2 days

* The symbols +, ++ and +++ indicate, respectively, dyspnea on exertion only, dyspnea on exertion with slight dyspnea at rest and dyspnea at rest and dyspnea on exertion with moderate dyspnea at rest.

significantly by diuretics in seven of twelve observations and was increased in only one. Consistent changes in heart rate and oxygen consumption did not occur. The cardiac output per minute was increased in three observations, decreased in one and unchanged in eight. (Changes in this function of less than 10 per cent are not considered as significant.) In proportion to the metabolism, the cardiac output following the administration of diuretics was greater in five observations and less in one. No correlation existed between the changes in the cardiac output and the degree of clinical improvement.

Since significant changes in the cardiac output did not occur in eight of the twelve observations, one might be inclined to attribute the changes found in the four other instances to error. However, this is unlikely, for the method used to measure the cardiac output permits one to detect fallacious results, and the rather rigid criteria which were used were adequately fulfilled in those instances in which well marked changes in the cardiac output occurred. Another explanation for the results obtained is that diuretic drugs have two different actions, the one tending to increase and the other to decrease of the output of the heart. In order to study this possibility additional observations were made.

Two patients who exhibited fluctuations in the cardiac output following the administration of diuretics were studied over a period of several weeks, no therapy being employed other than diuretic drugs, sedatives when needed and digitalis, the daily dose of which was kept constant. Observations on one of these patients during three successive "breaks" are shown in chart 2. In May, diuresis was associated with a slight increase in the cardiac output in proportion to the metabolism, as shown by a decrease in the arteriovenous difference, although the actual cardiac output declined. In June, diuresis was associated with an initial increase, followed by a marked decrease, in the arteriovenous difference. When, in July, diuretics were withdrawn and the patient was given an abundance of fluids, reaccumulation of edema was associated with an increase, followed by a decrease, in the arteriovenous difference. Diuresis was again accompanied by a decrease, and then by an increase, in the cardiac output in proportion to the metabolism. (In this man, who has repeatedly shown a marked increase in oxygen consumption during congestive heart failure, the arteriovenous difference is more reliable than the cardiac output as an index of the blood supply to the tissues.) The alterations depicted in chart 2 are compatible with the idea that two opposing factors, the one tending to increase the blood supply to the tissues and the other tending to have the reverse effect, are acting on the vascular system when edema is gained or lost.

In an attempt to distinguish between the possible peripheral and cardiac actions of diuretics, observations have been made of the oxygen utilization of the blood passing through the legs. Following the usual

measurements of the oxygen consumption and of the arteriovenous oxygen difference, samples of blood were drawn from the femoral vein and from the brachial artery. Analyses of the oxygen content were then made with the Van Slyke manometric apparatus. These observations are shown in charts 3 and 4. In one subject (chart 4), the oxygen utilization as determined on blood from the femoral vein first decreased and then steadily increased as diuresis occurred. The other patient

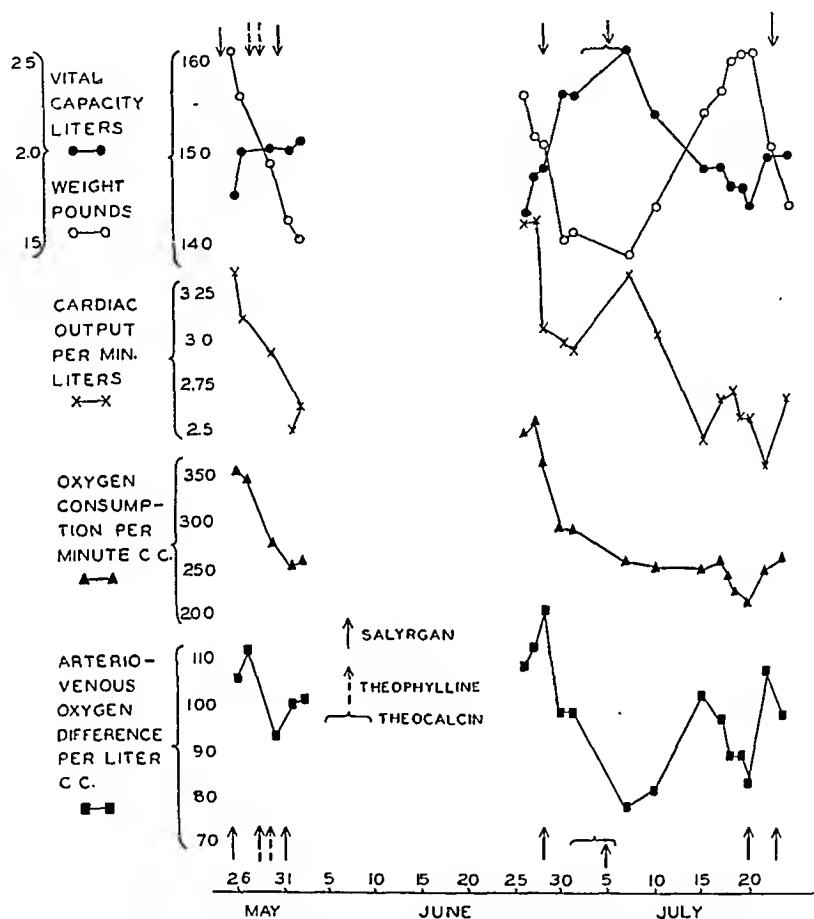


Chart 2.—Fluctuations in cardiac output following the administration of diuretics to a man (F. B.) with syphilitic aortic insufficiency.

(chart 3) likewise exhibited an increase in the arteriovenous oxygen difference of the blood passing through the leg as edema decreased. One of the patients had a striking decline in the general oxygen utilization; the changes in this function were inconstant in the other patient. Both patients exhibited a marked increase in the arteriovenous oxygen difference of blood from the femoral vein as compared with the general arteriovenous oxygen difference. These results indicate that in proportion to the metabolism a greater proportion of the blood pumped by the heart passed through the legs when edema was present than when

it was absent. These results are similar in general to those reported by Harrison and Pilcher.³ Our actual values for oxygen utilization in the legs are considerably greater than theirs. Probably this difference is to be attributed to the conditions under which the observations were made. Their patients were studied while semirecumbent in bed; ours were sitting upright in wheel chairs. As compared with the other tissues of the body, it appears that edematous tissues have a relatively great blood supply. One effect of diuretics, then, is to tend to diminish the

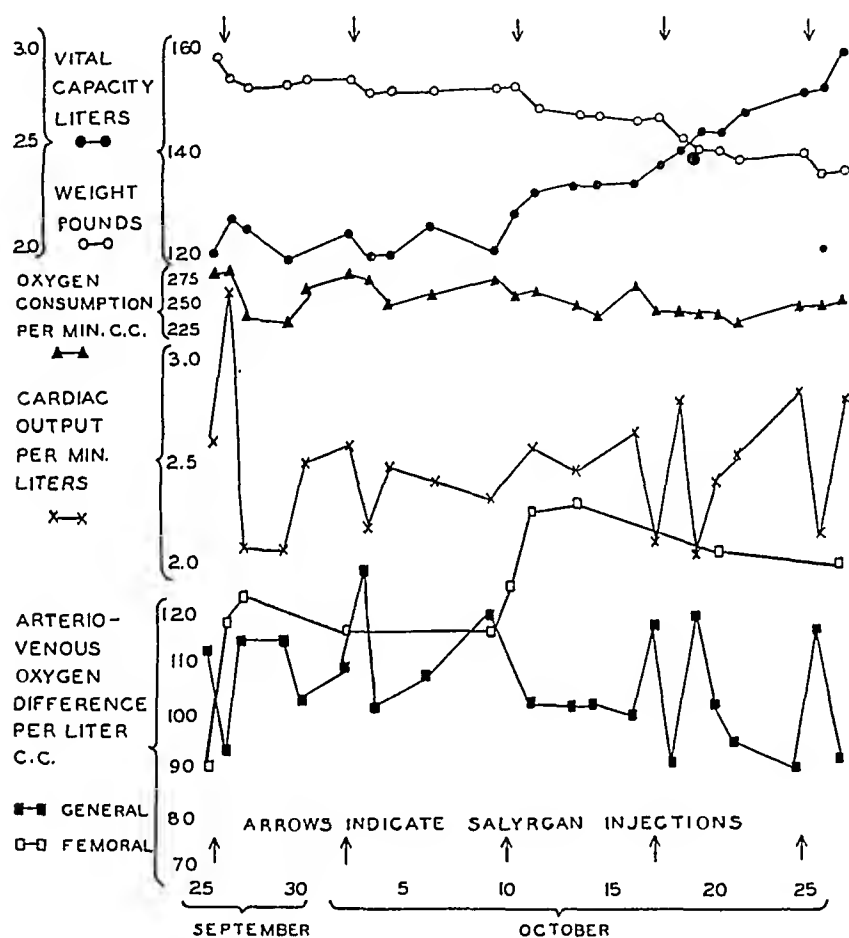


Chart 3.—Increase in the arteriovenous oxygen difference of the blood passing through the leg as edema was lost following injections of salyrgan in a man (F. B.) with syphilitic aortic insufficiency.

flow of blood through the edematous tissues. If other conditions remain constant, such an action will tend to decrease the cardiac output. The diminution in cardiac output and the increase in arteriovenous oxygen difference which sometimes follow the administration of diuretics are probably related to a peripheral effect secondary to loss of edema (table 1 and charts 3 and 4).

3. Harrison, T. R., and Pilcher, C.: Studies in Congestive Heart Failure: I. The Effect of Edema on Oxygen Utilization, *J. Clin. Investigation* 8:259, 1930.

Such a conception may account for a decline in cardiac output but does not explain the increase in this function which occurred following diuresis in many instances (table 1 and charts 3 and 4). With a constant pulse rate, the output of the heart may become greater either because of an augmented venous return or as a result of an increase in the contractile power of the heart. In our studies venous pressure was not measured, and hence we are unable to state with certainty that peripheral factors were not responsible for the increase in cardiac output. However, this seems unlikely on a priori grounds; furthermore,

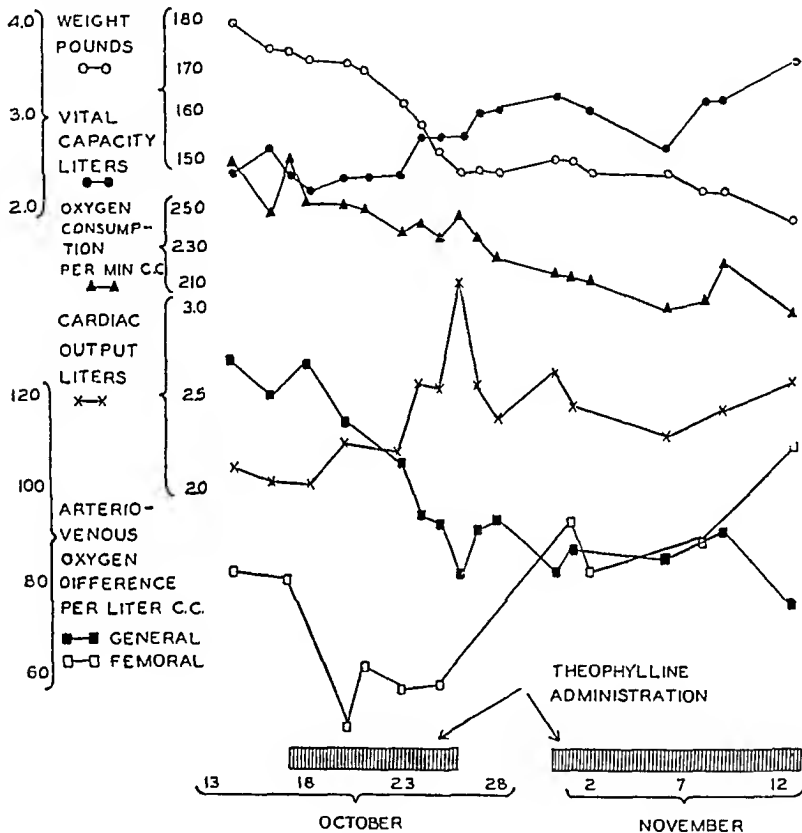


Chart 4.—Decrease and then increase in oxygen utilization as determined on blood from the femoral vein as diuresis occurred following injections of theophylline in a patient (A. M.) with syphilitic aortic insufficiency.

Harrison⁴ found that the venous pressure of persons with congestive heart failure often, although not always, diminishes following the administration of diuretic drugs. Is it likely, then, that the rise in cardiac output is dependent on an increase in the contractile power of the heart? In the case of theophylline such an action might be the result of the augmentation of the coronary flow of blood which is produced by the xanthine group of drugs. However, there is no evidence that salyrgan,

4. Harrison, W. G., Jr.: Personal communication.^{1c}

which may cause an increase in the output of the heart when it produces diuresis (chart 3), has any action on the coronary flow of blood.

Another possible explanation for the increase in cardiac output which has sometimes been observed after the administration of diuretics is as follows: Nielson and Palm⁵ found that a frog's heart, which following artificial perfusion had begun to fail, was restored by perfusion with blood serum. Since no beneficial effects were observed when an ultrafiltrate of serum was used, it was believed that the restorative action of serum was dependent on its proteins and was brought about by withdrawal of water from the cardiac muscle into the perfusing fluid. It is well known that persons dying of congestive heart failure often exhibit myocardial edema. The water content of the heart in such conditions often is increased and the content of solids correspondingly diminished (table 2). It is conceivable that diuretic drugs may

TABLE 2.—*Content of Solids of the Right and Left Ventricles of Persons Dying With Congestive Heart Failure and of Persons Dying Without Cardiac Disease*

Authors	Number of Patients Studied		Content of Solids of Right Ventricle, Percentage				Content of Solids of Left Ventricle, Percentage			
	Control Patients	Patients with Cardiac Disease	Control Patients		Cardiac Disease		Control Patients		Cardiac Disease	
			Range	Average	Range	Average	Range	Average	Range	Average
Calhoun, Cullen, Clark and Harrison: J. Clin. Investigation 9 : 696, 1931	3	13	21.0 to 18.6	20.0	20.3 to 17.6	18.6	23.0 to 19.9	21.8	22.0 to 17.6	19.5
Wilkins and Cullen: J. Clin. Investigation 12 : 1063, 1933	5	8	23.1 to 18.8	20.8	21.8 to 16.4	18.5	22.0 to 19.9	21.1	21.1 to 17.9	19.5

reduce edema in the heart muscle and that such an action may make the heart a more efficient pump and so enable it to respond to a given venous pressure with a greater output. The latter change is significant, not from the standpoint of increased blood supply to the tissues, but as an indication of an increase in the reserve power of the heart.

The foregoing discussion may be summarized by saying that diuretics may possibly have a twofold action on the circulation: 1. Reduction of peripheral edema may be associated with a decrease in the flow of blood through edematous tissues in proportion to the metabolism. The resulting decline in venous return and in venous pressure tends to decrease the output of the heart. 2. Reduction of myocardial edema may lead to an increase in the contractile power of the heart and con-

5. Nielson, N., and Palm, D.: Beiträge zur Kenntnis der Bedeutung der Serummikolloide für die Herztätigkeit, Skandinav. Arch. f. Physiol. **55**:41, 1929.

sequent increase in output. The final result may be a rise, a fall or no change in cardiac output. The important point is that diuretic drugs appear to aid the heart by: (a) decreasing its load and (b) increasing its ability to carry the load. Either of these effects tends to produce benefit by diminishing the energy expended by the heart.

COMMENT

The chief therapeutic measures which are commonly employed in the treatment of chronic cardiac disease are rest and digitalis. Diuretics usually are reserved for the advanced stages when dropsy has become pronounced. The studies of the circulatory and respiratory functions which have been presented indicate, we believe, that diuretic drugs may be of considerable benefit to patients who have minimal or even undetectable edema. For a number of years we have employed them for this purpose, and the fact that they may have an effect on circulation appears to afford a rational basis for their use. Whenever rest, reduction of the intake of fluids, digitalis and sedatives fail to produce clinical improvement in patients with congestive heart failure, diuretic drugs, we believe, should be given a trial, even though there may be no obvious subcutaneous edema.

SUMMARY

Diuretic drugs, even when administered to patients with minimal edema, often produce marked relief from dyspnea. The vital capacity is frequently increased following their administration.

Constant effects on the cardiac output have not been observed following the administration of these drugs. Occasionally the output is diminished. This effect is believed to be due to loss of peripheral edema, for the blood supply of edematous tissues is, in proportion to their metabolic needs, often relatively greater than the blood supply to the tissues in general. In some instances the cardiac output is increased by diuretic drugs. This effect is believed to be dependent on an action of these drugs on the heart and possibly to be related to loss of edema from the cardiac musculature. In many instances the administration of diuretic drugs is followed by no demonstrable change in the cardiac output. In such instances it is believed that the peripheral and cardiac actions of the drugs tend to neutralize each other. In favorable circumstances diuretic drugs appear to cause benefit both by tending to decrease the load on the heart and by increasing the ability of the heart to carry its load.

The foregoing evidence is interpreted as indicating that diuretic drugs are of more than symptomatic value. They should be employed frequently for ambulatory patients who have minimal edema or who are suspected of having latent edema.

TEACHING MEDICAL STUDENTS OBJECTIVES FOR CARE OF PATIENTS AND SOCIAL ASPECTS OF ILLNESS

ETHEL COHEN, M.S.
AND
HARRY A. DEROW, M.D.
BOSTON

It is the effect upon him [the patient] singly or collectively, which is the final test of the worth of any and every part as well as the whole of medical science. In the crowded times of new discoveries and of the development of more and more accurate means of diagnosis, we may perhaps find our excuse in having forgotten the object of it all—the patient himself. However that may be, the fact is, that from about the time of Lister to almost the present day, forgotten he has been. During this period, the study of disease, not of patients, has been the object of most of our best endeavor. But now the rediscovery of the patient as the most important item in the picture has changed all that, and the new generation of physicians can now, at the very beginning of their careers, go forth with the brand new but very old fashioned and sane objective of helping their patients to avoid illness, to overcome illness, or failing this, to die with as little suffering as possible. To this end, scientific methods, the laboratories, and all other means become the ready servants of the art of medicine. But the Art itself will be blind unless it is guided by an understanding of the individual patient and, furthermore, of the significance to him both of his illness and of his treatment.¹

Although this ideal is ably expressed by Dr. Riggs and shared by many leaders of the medical profession,² in general, insufficient consideration is given to the total needs of the patient. This is due to the tendency to plan only in terms of the present situation without taking a long-range view of the entire problem. Impersonal stereotyped advice for a change of regimen is frequently given without regard to the social elements which may render such advice entirely impracticable. To overcome this defect a plan³ known as “Medical Social Ward Rounds” was evolved at the Beth Israel Hospital to train young physicians during their internship. Because of the contribution of this

From the Medical and Social Services, Beth Israel Hospital.

1. Riggs, A. F.: The Significance of Illness, in Emerson, L. E.: The Physician and Patient, Cambridge, Mass., Harvard University Press, 1929, p. 101.

2. (a) Edsall, D. L.: Some of the Human Relations of Doctor and Patient, in Emerson, L. E.: The Physician and Patient, Cambridge, Mass., Harvard University Press, 1929, p. 3. (b) Minot, G. R.: The Physician, Student and Social Worker, Boston M. & S. J. **193**:1090 (Dec. 10) 1925. (c) Means, J. H.: The Social Component in Medicine, Hosp. Social Serv. **24**:74, 1931.

3. Derow, H. A., and Cohen, E.: The Training of Interns in the Social Aspects of Medicine, New England J. Med. **209**:827 (Oct. 26) 1933.

procedure to the development of the intern it was believed that it might be profitable to the student to give him a similar type of experience during his period as an undergraduate in the medical school.

For a number of years the teaching of the social implications of disease has been developing.⁴ Since the opening of the Beth Israel Hospital in 1928 several different methods have been tried and discarded. In 1933 and 1934 an entirely new plan of teaching was developed, and that plan is being reported at this time because of its effectiveness in stimulating the students' interest. It consisted in correlating the purely medical aspects of a disease with an interpretation of the significance of the disease and its treatment in the life of the individual patient. In addition, especial emphasis was placed on the formulation of specific objectives for the care of patients.

OUTLINE OF PLAN

Scope of Teaching.—Seminars lasting from two to two and one-half hours were conducted jointly by a medical instructor and a medical social worker in an office of the hospital. Successive groups of from three to nine students of the fourth year classes of Harvard University Medical School and Tufts College Medical School participated. Each student from Harvard University Medical School attended four sessions, and each student from Tufts College Medical School attended only two sessions because of the shorter period of assignment at this hospital. Fourth year students were chosen rather than third year students because the clinical training which students received in the third year served as a preparation for this type of analysis and evaluation.

Each seminar included (1) a review of the medical aspect of a certain disease, (2) a discussion of general objectives for the care of patients with the disease under consideration, (3) the presentation of several patients with the disease under consideration, (4) a discussion of the specific means of achieving the objectives outlined and (5) a recapitulation of the salient factors.

Instructors' Preparation for Seminars.—Each seminar required considerable advance collaboration and preparation by both instructors. The choice of diseases, the selection of patients, the study of records and an outline of the material to be presented were made jointly. Arthritis, asthma, carcinoma, cardiac disease, peptic ulcer, rheumatic infection and tuberculosis were discussed. Two or three patients were selected from the ward and from the medical instructor's private practice to illustrate the various types of problems found in a certain disease

4. Cannon, I. M.: Teaching Medical Students the Social Implications of Illness, New England J. Med. **211**:216 (Aug. 2) 1934. Minot.^{2b}

in both its chronic and its acute aspects. Patients from private practice were included to demonstrate that these problems exist not only in hospital wards but also in private practice, regardless of the patient's social or economic status.⁵

After the patients had been selected from the ward each instructor read the medical records of which the social history prepared by the student was a part. The medical instructor also made his own examination of the patients. The social situation and the possibilities for executing the medical recommendations were ascertained from the social worker's record and from visits to the patient's home made by a social worker.

After the records had been studied and before the opening of the seminar an outline was prepared jointly by the instructors to insure continuity in presentation of the subject matter. Decisions were then made as to the subjects in the outline which each instructor would present. The instructors prearranged the questions which they would ask the students during the seminar for the purpose of stimulating general discussion. It was agreed that the medical instructor would assume responsibility for essentially medical questions and the social worker that for questions on social aspects. Each instructor was expected to supplement the remarks of the other. It was planned to encourage the students to raise questions and to make comments at all times during the seminar, even if the instructors' planned presentation was interrupted.

METHOD OF PROCEDURE

A typical seminar was conducted in the following manner:

1. *Review of the Medical Aspect of the Disease.*—The medical instructor presented a review of a specified disease. This included a discussion of the etiology and of methods of establishing a diagnosis, the presentation of an outline of the natural course of the disease and a discussion of the method of estimating the prognosis for the duration of life and the amount of activity that might be permitted with and without treatment. During this review of the medical aspect of the disease the medical instructor by direct questioning sought every opportunity to foster the students' participation.

2. *Discussion of Objectives for the Care of the Patient.*—After the review of the medical aspect of the disease there was a discussion of objectives for the care of patients with the disease. The objectives which had particular application to the disease under consideration were selected from the following list: (1) to restore the patient to complete health, (2) to restore the patient to the usual state of health, (3) to pre-

5. Minot, G. R.: Medical Social Aspects in Practice, Arch. Int. Med. 54:1 (July) 1934.

vent a recurrence of the disease, (4) to increase the patient's tolerance to the disease, (5) to effect a maximum amount of rehabilitation, (6) to arrest the progress of the disease, (7) to retard the progress of the disease and (8) to palliate an incurable progressive disease.

Restoration to complete health may be an impossible goal after an acute exacerbation of a chronic disease. The patient, however, may be restored to his usual state of health which, though impaired, may be the best state possible for him. There are times when the physician aims for more than one objective. For example, in the case of tuberculosis the immediate aim is to arrest the progress of the disease. A second aim is to restore the patient, if possible, to complete health. A third aim is to prevent recurrence of the disease in the patient, and another, broader, aim is to prevent its spread in the community. In cases of chronic arthritis the aims are to effect the maximum amount of rehabilitation, to arrest the progress of the disease and at the same time to increase the patient's tolerance to the disease.

It was demonstrated that the objectives for care also vary according to the stage of the disease at which the physician is making recommendations. For example, the aim in the care of a patient with an early stage of carcinoma of the breast would be restoration to complete health and prevention of recurrence, while in the case of a patient with a moderately advanced stage of carcinoma of the rectum the aim might be retardation of the progress of the disease. The only possible objective in a case of inoperable carcinoma of the stomach would be to palliate this incurable progressive disease.

After the discussion of objectives came the important question of the means to be used to bring about their achievement. It was shown how these objectives could be realized through utilization of the resources of the patient or of the community.

3. *Presentation of Patients.*—The general review of the medical aspect of the disease, the formulation of objectives and the consideration of the means of attaining them served as a background for the presentation of individual patients selected from the ward and from private practice because of their particular medical and associated problems.

The patients from the wards were well known to the students through the daily morning teaching visits. To save time the medical instructor, rather than the student, briefly outlined the history and present illness of one of these patients. The significant features of the case were graphically demonstrated by use of the patient's medical record and roentgenograms. A complete study of the case had already been made by one of the students. This included a consideration of the patient's racial background, emotional life, intellectual capacity, habits, attitudes, recreation and environment, economic status, occupation, facilities for after-care, etc.

After the instructor had presented the medical aspects the student who had studied the case described the patient's present condition and made recommendations for the patient's care. He was challenged by both instructors and by other students to state the basis for these recommendations. Objectives for the care of the individual patient were considered in the same way in which objectives had been discussed by the medical instructor in considering the disease entity. The social worker at this point asked how the recommendations could be carried out. First the student who studied the case proposed a plan. Then the other students either concurred in this plan or offered other plans. At this phase of the discussion came the opportunity for the social worker to point out the relationship between social factors and illness, in that the former are the cause of illness, a complicating element or the result of it.

For example, a student might make a recommendation for light work and freedom from emotional strain without realizing that the hypertensive patient for whom those suggestions were made was a mother of five small children, had burdensome household responsibilities and was in straitened financial circumstances. Similarly, the student might offer the simple suggestion of rest in bed for a patient with cardiac disease. In that case close inquiry by the social worker might reveal that the student had given no thought to the many elements involved for some persons in securing rest in bed. In a case in which rest in bed at home was impossible because of overcrowded housing and lack of necessary attention the student might suggest the alternative of placing the patient in a nursing home, a suggestion made without regard for the need of payment for such care, for the source of funds to provide it or for the methods by which such funds might be made available. A change to some light occupation might be proposed for an illiterate longshoreman incapacitated by infectious arthritis. Such change of occupation might be desirable, but the student failed to realize the futility of suggesting light work for an unskilled, middle-aged illiterate man, since it is usually impossible to find such work for a patient of this type. A blanket recommendation for placing the patient in a municipal sanatorium might be made for a tuberculous patient with disregard of the fact that if it were carried out serious problems would arise if the patient were a recent immigrant with no claim to governmental care, subject to deportation to a country from which he was a political refugee. The suggestion of a change of climate for a 40 year old rag-sorter, the head of a family of six, with severe bronchial asthma, might be made seriously with no consideration of obstacles involved, namely, the cost of transportation, maintenance in a strange, distant community, separation of the patient from his family and the support and management of that family.

In cases such as those mentioned the social worker with no information other than that provided by the student was sometimes able to demonstrate the nonfeasibility of the plan suggested because of her better correlation and more thorough interpretation of the data already known.

Why did the students fail to take all these facts into consideration? Was it because of the inadequacies of the histories that they had obtained? As a matter of fact, the histories were usually complete and accurate. The difficulties seemed to be due to the tendency to make the taking of the history a matter of routine unassociated in the students' minds with the realities confronting a certain patient, as well as to the failure to coordinate the facts gleaned during the taking of the history with the plan for treatment.

4. *Discussion of the Specific Means of Achieving the Objectives Outlined.*—In some cases a plan for after-care as suggested by the student was perfectly appropriate so far as the disease itself was concerned, yet was not practicable because of the student's failure to evaluate the individual patient's resources. In such cases the reasons for the impracticability of the plan suggested were pointed out by the social worker through her analysis of the data provided by the medical student and by her own investigation.

In some cases the student fully appreciated the inadequacy of the patient's resources but was unable to make a reasonable suggestion for future care because of his ignorance as to the existence of suitable community resources and the means of regimenting them in behalf of the patient.

The fourth part of the seminar included an explanation by the social worker that often the assistance of the department for social service of a hospital or of some other social agency is needed (1) to help patients analyze and evaluate their own resources and utilize them effectively, (2) to indicate to patients capable of self-direction the availability of community resources or (3) to execute for patients incapable of self-direction a plan of treatment which includes the use of community resources.

By discussing a certain disease in several patients, each of whom presented a different social situation, the various types of resources which might be needed were demonstrated.

The students were shown a copy of the "Physician's Handbook of Community Resources in Metropolitan Boston,"⁶ which describes the medical, health and social resources available to patients in metropolitan Boston. As some students would practice in communities outside of

6. Physician's Handbook of Community Resources in Metropolitan Boston, published under the auspices of the Massachusetts General Hospital, Boston, 1933.

Boston it was suggested that they secure advice as to resources in their prospective communities from social service departments in hospitals or from local councils of social agencies.

The need for physicians to stimulate the development of additional resources, wherever such resources are lacking, was also brought out. The students took a lively part in this portion of the discussion, particularly the students from communities outside of Boston which are not highly organized from the point of view of social welfare.

The discussion of community resources led to a more general consideration of the responsibility of the community for the care of the sick and the economic cost of illness. Because of the diversity of their personal experiences and their philosophies of life, the students expressed a variety of opinions regarding (1) the patient's responsibility for meeting his own health needs, (2) the responsibility of relatives and employers, (3) the responsibility of the community for the care of the sick, etc. These opinions were discussed and evaluated by the two instructors, each contributing from the experience in his or her own field.

5. *Recapitulation of the Salient Factors.*—The seminar was concluded with a recapitulation by both instructors of the salient factors which had arisen in the consideration of the concrete problems of the patients discussed. The variation in plans for the treatment of different patients with the same disease was shown to be due to the factors of residence, racial background, religious scruples, emotional reactions, psychologic attitudes, intellectual endowment or any other component part of the social situation. The problems of patients from the wards were paralleled by the problems of the private patients of the medical instructor, and it was shown that, regardless of the more favorable economic and social status of private patients, the need still existed for adjustments of environmental, psychologic or emotional factors.⁵

The social worker reviewed in a general way the social implications of illness, the broad concept of the care of the patient rather than merely the treatment of a diseased organ. The medical instructor pointed out that it is important that the physician have clearly in mind what his objectives should be in the care of each patient, the value of appreciating and dealing with social obstacles that often prevent the achievement of these broad objectives and the need of calling on expert service in the community in various fields to assist in the attainment of his goal.

COMMENT ON METHOD OF PROCEDURE

The conferences were informal seminars conducted jointly by a physician and a medical social worker. Two seminars for each group seemed insufficient; four sessions gave more satisfactory results. It is

believed that six such meetings would afford greater opportunity to establish this type of thinking more firmly.

The teaching of the social component in illness, it was believed, could be handled best as a part of a medical exercise rather than as a separate isolated conference on social service. In preparing the outline and in conducting the seminar the instructors made a conscious effort to prevent devoting a disproportionate amount of time to the essentially medical discussion.

Experience demonstrated that the consideration of a single disease during one session of a seminar was more effective than the discussion of several diseases. The diseases which seemed to be of paramount importance, because of their incidence and their special medical and social implications, are arthritis, carcinoma, peptic ulcer, rheumatic infection, cardiac disease, syphilis and tuberculosis. These diseases, it is believed, should constitute the minimum considered by each group, although acute self-limited diseases present significant problems and should be included, if possible.

The students were asked to express their reactions to this experiment in teaching. There was general agreement that the review of the medical aspect broadened their concept of the disease itself by summarizing and unifying for them in a new way information which they had previously acquired in scattered parts of their curriculum. For the first time they realized that the presenting illness was only one episode in the natural history of a disease and that this episode as well as possible later complications had to be considered in making adequate plans for the care of the patient.

The discussion of objectives was an entirely new experience for the students, as they were obliged to voice their actual aims for the care of the patients. In the formulation of objectives for care and the planning of their achievement, special significance was necessarily placed on the patient and his needs rather than on the narrower concept of his disease. The students believed: (1) that a preliminary general discussion of a given disease served as a valuable background for the later presentation of concrete problems of individual patients with the same disease, (2) that such a discussion was a natural approach and conforms with their other clinical teaching and (3) that this method made the integration of the medical and social factors more effective and should permanently influence their future care of patients.

SUMMARY

A method of teaching medical students objectives for the care of patients and the social aspects of illness is presented.

The purpose was to demonstrate the need for physicians to give full consideration to the patient and his illness instead of placing exclusive emphasis on the disease.

The habit of giving such thought to patients may be established in medical students by the formulation of concrete objectives for the care of each individual patient and by the realization that to attain these goals the consideration of certain social and psychologic factors must be integrated into the whole process of medical study and treatment.

It is believed that the teaching of this subject should be carried on as a medical exercise conducted jointly by a physician and a medical social worker.

INCREASED EFFECTIVENESS OF INSULIN WHEN GIVEN BY INJECTIONS OF DOSES OF EQUAL UNITAGE AT INTERVALS OF TWO TO FOUR HOURS

I. USE OF INSULIN IN DIVIDED DOSES TO MANAGE SEVERE UNCOM- PLICATED DIABETES AND TO CONTROL COMPLICATED MEDICAL CASES

BYRON B. CLARK, PH.D.

R. B. GIBSON, PH.D.

AND

WILLIAM D. PAUL, M.D.

IOWA CITY

The administration of insulin in divided doses, i. e., in injections of doses of equal unitage at two to four hour intervals day and night, was first used at University Hospitals in 1929 as an emergency post-operative measure. The results were sufficiently encouraging, and a further experimental study was made on 11 patients with uncomplicated diabetes in 1929-1930. These experiments indicated that insulin given in divided doses is much more efficient; that much less insulin is required; that the blood sugar level is more easily kept within satisfactory limits; that the glycosuria is more quickly controlled, and that hypoglycemic reactions rarely occur. The procedure has been of such great value that it has become a routine measure in managing severe uncomplicated diabetes which is difficult to control with two or three daily injections of insulin, in treating diabetes with associated acute infections and in handling postoperative cases. Of the 1,553 patients admitted to the diabetic service during the past five years, 146 have been treated with divided doses; 74 had severe uncomplicated diabetes and 72, complications, which were usually surgical.

METHOD

Either on admission or as soon thereafter as complications would permit the patients were placed on a maintenance diet of the Woodyatt type, e. g., protein, 60 Gm., carbohydrate, 60 Gm., and fat, 150 Gm.—calories, 1,887. The diet was ordinarily kept constant during the period of hospitalization. Determinations of the blood sugar content ¹ were usually made before the patient's admission to the hospital

From the Laboratory of Pathological Chemistry and the Department of Internal Medicine, University Hospitals, the State University of Iowa.

1. Gibson, R. B.: The Micro Determination of Blood Sugar, *Proc. Soc. Exper. Biol. & Med.* **27**:480, 1930.

and thereafter at 9 a. m., two hours after breakfast, and at other times as indicated. Twenty-four hour specimens of urine were examined daily for diacetic acid and sugar. The type of dosage of insulin as well as the amount depended on the diabetic and clinical condition of the patient.

Usually in uncomplicated medical cases an attempt was made to control the diabetes with the regular dosage of two or three daily injections of insulin. If after a few days with a reasonably high dosage of insulin the blood sugar level remained high or glycosuria persisted, a regimen of divided doses was instituted. In a number of cases regarded as experimental, a routine of divided doses was instituted after satisfactory management had been achieved in order to compare further the efficiency of the two types of dosage. Patients with acute infections were usually placed on a regimen of divided doses immediately on admission or at the time the infection developed. The length of the period of divided dosage varied from a few days to a month or even longer. Then the regular dosage was resumed. The treatment in cases of acidosis differed only in the initial stages of management, when repeated large doses of insulin were given intravenously with dextrose in physiologic solution of sodium chloride. As soon as the acute symptoms of the acidosis had subsided and the blood sugar reached a reasonable value, divided doses were started.

In surgical cases, except those requiring almost immediate operation, the condition was managed in the usual way, with diet and regular dosage of insulin. Two hours preoperatively the patient was given additional insulin and dextrose and divided doses were administered postoperatively whether he was able to take food or not. In the event of continued inability to ingest food and following certain surgical procedures, such as cholecystectomy, dextrose was given intravenously by hypodermoclysis or rectally either with or without additional insulin, usually depending on the condition of the patient, the amount of dextrose given and the mode of administration. When intravenous injections of dextrose were repeated over a period of several days, it was usually unnecessary after the first two or three injections to give additional insulin beyond that received in divided doses. These patients were usually given divided doses until they had recovered from the surgical procedure. In cases in which immediate operation was required, the initial procedure was to give insulin and dextrose intravenously, and divided doses were started immediately postoperatively.

Representative cases are described in detail in the accompanying case reports and tables.

RESULTS

We have uniformly observed that for patients with uncomplicated diabetes on a constant diet the requirement of insulin given in two or three daily injections can be reduced by as much as one third to one half when divided doses are given. Patients with a condition difficult to control responded satisfactorily on this regimen. It was of special interest to note that although the injections of insulin were given irrespective of meals the blood sugar level, while higher after breakfast, tended to decrease following the noon and evening meals and to be low during the night. However, in spite of the low blood sugar level which obtained at night, hypoglycemic symptoms were rarely encountered; reactions were more likely to occur during the day or early evening and were not so severe as those following large injections of insulin. To obviate the possibility of reaction, one injection, usually at midnight, was

omitted; but there were some cases in which it was necessary to include all the injections to keep the blood sugar level in the morning reasonable and the urine free from sugar. Patients treated with divided dosage remained resistant to hypoglycemic symptoms when the usual management was resumed. The tolerance of patients with severe uncomplicated diabetes tended to improve more rapidly (i. e., the insulin requirement was reduced) when given the divided dosage than when they received the usual type of dosage. On resumption of the regular dosage these patients required either the same amount of or, more often, more insulin. The gain in tolerance which they had shown while receiving divided doses was usually only in part sustained. Diet seems to be a factor in the success of the regimen of divided doses, as indicated by the fact that in some cases in which the diet was supplemented with an increased amount of carbohydrate there was a definite tendency to a lower requirement of insulin during the day and early evening than during the night and early morning. However, in a number of other cases in which a diet high in carbohydrate was used the use of divided dosage was satisfactory.

After surgical intervention patients for a time usually required larger amounts of insulin with divided dosage, but following recovery from the surgical procedure they usually showed such a marked improvement in tolerance that when regular dosage was resumed they required either the same amount of or, frequently, less insulin. The use of divided doses has been of exceptional value in carrying these patients through the postoperative crisis, and the postoperative course was usually uneventful and quite satisfactory.

Patients with complicated medical cases recovering from the acute stage of the disease had requirements of insulin similar to those of patients with surgical cases. The former required the same amount of or, more frequently, less insulin when the usual management was resumed after a regimen of divided doses. Control of their diabetes during the acute stage of the disease was much more satisfactory following the use of divided doses.

COMMENT

The data suggest a rather constant and continuous secretion of insulin on the part of the islet cells of the pancreas which would explain the increased efficiency of insulin given in divided doses.

Certain facts in the literature and common observations in the clinic for the treatment of diabetic patients indicate that such an explanation is rational. A direct relationship between the amount of insulin required to metabolize and store a definite amount of dextrose has not been satisfactorily demonstrated. A latency or long continued action of insulin has been observed in two respects: (1) the delayed or prolonged

effect of insulin which has been injected, and (2) a latent period in both the diabetic subject when deprived of insulin and the depancreatized dog before the development of maximal diabetes. Soskin and Allweiss² have demonstrated a normal curve for blood dextrose following the injection of dextrose into completely depancreatized dogs receiving a continuous intravenous injection of dextrose and insulin to maintain a constant blood sugar level. In such experiments they have also been able to show the hypoglycemic phase occurring at the end of the curve.³ Recently Ellis⁴ has shown a marked temporary improvement in tolerance in patients with severe diabetes by giving hourly administrations of insulin and dextrose. This improved tolerance, however, was not permanently sustained after the patients returned to their usual diets and regular dosage of insulin. Ellis also made one or two experiments in which hourly injections of insulin were used for patients on ordinary diets. The observations indicated an increased efficiency of the insulin with frequent injections. That the increased efficiency even in part is not accounted for by the excretion of some of the large doses in the urine is indicated by the failure to demonstrate the presence of insulin in the urine of such patients (Ellis,⁴ Ueberrack and Zell⁵ and the experiments of one of us [B. B. C.]).

One may assume, then, that the more or less constant and continuous secretion of insulin is adjusted to the habitual intake of carbohydrate. The effect of various diets on the dextrose tolerance has been shown by Sweeney⁶ and has been confirmed repeatedly. Whether the ability to store and metabolize a supply of dextrose above the usual intake, as demonstrated in normal subjects by Hamman and Hirshman⁷ and in diabetic patients by Gibson⁸ in this hospital and by Ellis,⁴ is due to

2. Soskin, S., and Allweiss, D.: Factors Determining the Dextrose Tolerance Curve, *Am. J. Physiol.* **105**:89 (July) 1933. Soskin, S.; Allweiss, M. D., and Cohn, D. J.: Influence of the Pancreas and Liver upon the Dextrose Tolerance Curve, *ibid.* **109**:155 (July) 1934.

3. Soskin, S., and Allweiss, M. D.: The Hypoglycemic Phase Following the Normal Dextrose Tolerance Curve, *Am. J. Physiol.* **109**:101 (July) 1934.

4. Ellis, Arthur: Increased Carbohydrate Tolerance in Diabetics Following the Hourly Administration of Glucose and Insulin Over Long Periods, *Quart. J. Med.* **3**:137, 1934.

5. Ueberrack, K., and Zell, F.: Ueber das Vorkommen von Insulin im Harn, *Biochem. Ztschr.* **239**:42, 1931.

6. Sweeney, J. S.: Dietary Factors that Influence the Dextrose Tolerance Test, *Arch. Int. Med.* **40**:818 (Dec.) 1927.

7. Hamman, L., and Hirshman, I. I.: Studies on Blood Sugar: IV. Effects upon the Blood Sugar of the Repeated Ingestion of Glucose, *Bull. Johns Hopkins Hosp.* **30**:306, 1919.

8. Gibson, R. B.: Latent Tolerance in Diabetes Mellitus: A Study of the Effect of High Sugar Diets with Insulin on Controlled Diabetics, *J. Lab. & Clin. Med.* **14**:597, 1929; Further Observations on Latent Tolerance in Diabetics, *Proc. Soc. Exper. Biol. & Med.* **26**:449, 1929.

an increased secretion of insulin is not clear. There is some evidence that this is the case; nevertheless stimulated glycogenesis must be an important factor in the mechanism of sugar consumption. The experiments reported in this paper lend considerable support to Macleod's idea that insulin produces a "sugar vacuum" in the tissues.

In view of these observations, the administration of insulin in divided doses is a rational procedure more closely approximating the normal physiologic mechanism, and hence one expects the requirement of insulin to be less and the patient's tolerance to improve faster than when insulin is given in the usual way. The experimental observations entirely confirm these theoretical considerations.

CONCLUSIONS

1. Contrary to the usual procedure insulin may be given in injections of amounts of equal unitage at intervals of from two to four hours day and night irrespective of meals.

2. Insulin given in this way is much more efficient.

3. The blood sugar value is somewhat higher after breakfast, lower following the noon and evening meal and quite low during the night. Hypoglycemic reactions rarely occur.

4. The data suggest a rather constant and continuous secretion of insulin by the islet cells of the pancreas.

5. In patients with severe uncomplicated diabetes the condition is more easily controlled and there is a more rapid improvement in tolerance with divided doses than with the regular dosage.

6. When the regular dosage of insulin is resumed, the patients with uncomplicated medical cases require either the same amount of insulin or, more often, more; those with surgical cases showing rapid recovery usually require the same amount but frequently less.

7. The use of divided doses is of great practical importance in treating patients with severe uncomplicated diabetes, those with acute infections and those recovering from surgical intervention.

REPORT OF CASES

CASE 1.—O. P. (table 1), a youth aged 16, was admitted to the hospital on March 4, 1930, with severe diabetes which began suddenly in 1927 and which had been controlled at home by diet and later with insulin. In January 1930 he had pneumonia, following which the intensity of the diabetes increased and he was referred to the medical service for management. His only symptoms were those referable to the diabetes. The physical examination gave essentially negative results.

On admission the blood sugar content was 460 mg. per hundred cubic centimeters. The patient was placed on a diet of protein, 60 Gm., carbohydrate, 60 Gm., and fat, 150 Gm., equivalent to 1,887 calories. Regular insulin therapy was instituted at once. On March 10, the sixth day after admission, the diabetes was under

control, as judged by the blood sugar content and the diminished amount of sugar in the urine, with a dosage of 40 units of insulin before breakfast and 20 units before supper, a total of 60 units. On the following day he was given 4 units of insulin every two hours until ten injections were received (omitting the injections at 11 p. m. and 3 a. m.), making a total of 40 units. This resulted in a reasonable blood sugar value and the disappearance of sugar from the urine. On March 13, because of a reaction that evening, it was necessary to reduce the

TABLE 1.—*The Values for Blood Sugar in Case 1 with Insulin in Divided Doses*

Date	Urine Sugar	Blood Sugar, Mg.			Insulin Units		Comment
		9 A.M.	2 P.M.	7 P.M.	Dosage	Total	
3/ 4/30	460	...	-20	20	
3/ 5	4+	306	25-10-20	55	
3/ 6	—	281	30-10-20	60	
3/ 7	4+	241	40-10-20	70	
3/ 8	2+	217	107	78	40-10-20	70	
3/ 9	Trace	170	147	...	40- 0-20	60	
3/10	Trace	157	182	116	50- 0-20	60	
3/11	...	102	142	157	40- 4 every 2 hr.	56	Injection omitted at 11 p.m. and 3 a.m.
3/12	—	182	150	145	4 every 2 hr.	40	Injection omitted at 11 p.m. and 3 a.m.
3/13	Trace	281	122	78	4 every 2 hr.; 3 every 2 hr.	35	2 units every 2 hr. begun at 9 p.m.
3/14	—	192	138	186	3 every 2 hr.	30	Injection omitted at 11 p.m. and 3 a.m.
3/15	1+	231	179	167	3 every 2 hr.	36	
3/16	—	179	170	...	3 every 2 hr.	36	
3/17	—	176	162	157	3 every 2 hr.	36	
3/18	—	152	135	140	3 every 2 hr.; 2.5 every 2 hr.	33	2.5 units every 2 hr. begun at 3 p.m.
3/19	—	167	167	116	2.5 every 2 hr.	30	
3/20	—	147	90	114	2.5 every 2 hr.	30	
3/21	—	138	131	145	2.5 every 2 hr.; 2 every 2 hr.	27	2 units every 2 hr. begun at 3 p.m.
3/22	—	145	135	104	2 every 2 hr.	24	
3/23	—	145	170	105	2 every 2 hr.	24	Reaction at 3 a.m.; orange juice given
3/24	—	152	120	116	2 every 2 hr.; 2 every 3 hr.	22	2 units every 3 hr. begun at 10 p.m.
3/25	—	145	145	140	2 every 3 hr.	16	
3/26	—	162	145	142	2 every 3 hr.	16	
3/27	—	170	162	170	2 every 3 hr.	16	
3/28	—	179	150	170	2 every 3 hr.	16	
3/29	—	162	157	150	2 every 3 hr.	16	
3/30	—	173	...	147	2 every 3 hr.	16	
3/31	Trace	179	140	167	2 every 3 hr.	10	Last injection of divided doses at 4 p.m.
4/ 1	Trace	140	165	122	15- 0- 8	23	
4/ 2	Trace	204	196	147	15- 0-12	27	
4/ 3	—	131	162	66	20- 0-12	32	Reaction at 7 p.m.; orange juice given
4/ 4	..	104	20- 0- 9	29	Discharged

dosage of insulin to 3 units every two hours except at 11 p. m. and 3 a. m., making a total of 30 units. This was too great a reduction, however, for the blood sugar content rose; so the 11 p. m. and 3 a. m. injections were included, making a total dosage of 36 units a day. As the patient's tolerance improved, further reductions to 2.5 and 2 units every two hours and 2 units every three hours were made on March 18, 21 and 24, respectively. On March 30 the patient was receiving 2 units every three hours, or a total of 16 units. Injection of insulin twice daily was resumed on April 1, with doses of 15 and 8 units, which was insufficient; the proper dose was found to be 20 and 9 units, or a total of 29 units a day. On discharge the patient's diet was increased with fat to 2,450 calories.

CASE 2.—H. B. (table 2), a woman aged 25, was admitted to the hospital on March 16, 1933, with severe diabetes; polyuria, polydipsia, polyphagia and glycosuria were first observed in September 1931. At that time she was placed on a carbohydrate-restricted diet. Two months later she had acidosis followed by coma, during which insulin therapy was started; she continued to take insulin until her admission to the hospital, but her home management had not been satisfactory. The physical examination gave essentially negative results.

On admission the blood sugar content was 553 mg. The patient was placed on a diet of protein, 60 Gm., carbohydrate, 60 Gm., and fat, 150 Gm.—calories,

TABLE 2.—*The Values for Blood Sugar in Case 2 with Insulin in Divided Doses*

Date	Urine Sugar	Blood Sugar, Mg.	Insulin Units		Comment
			Dosage	Total	
3/16/33	4+	553	30	30	
3/17	4+	281	30-12-25	67	
3/18	...	226	40-12-25	77	
3/19	4+	281	40-15-30	85	
3/20	4+	99	40-15-25	80	Blood sugar reading taken at 2 p.m.
3/21	3+	237	37- 8 every 3 hr.	78	
3/22	1+	231	8 every 3 hr.	56	Injection omitted at 2 p.m.
3/23	—	173	8 every 3 hr.	64	
3/24	—	142	8 every 3 hr.	58	7 units injected from noon on
3/25	—	176	7 every 3 hr.	56	
3/26	1+	259	7 every 3 hr.	61	5 units added at noon
3/27	—	152	7 every 3 hr.	56	
3/28	—	204	7 every 3 hr.	56	
3/29	—	165	7 every 3 hr.	56	
3/30	—	138	7 every 3 hr.	56	
3/31	—	147	7 every 3 hr.	56	
4/ 1	—	145	7 every 3 hr.	56	
4/ 2	—	157	7 every 3 hr.	56	
4/ 3	—	105	7 every 3 hr.	56	
4/ 4	—	183	7 every 3 hr.	56	Blood sugar 107 mg. at 2 p.m., 131 mg. at 7 p.m., 37 mg. at 12 p.m., 44 mg. at 7 a.m.
4/ 5	—	167	7 every 3 hr.	56	
4/ 6	—	152	7 every 3 hr.	49	Dose omitted at 12 p.m.
4/ 7	—	109	7 every 3 hr.	49	Dose omitted at 12 p.m.
4/ 8	—	140	6 every 3 hr.	42	Dose omitted at 12 p.m.
4/ 9	—	162	6 every 3 hr.	42	Dose omitted at 12 p.m.
4/10	—	179	6 every 3 hr.	42	Dose omitted at 12 p.m.
4/11	—	138	6 every 3 hr.	42	Dose omitted at 12 p.m.
4/12	Trace	173	6 every 3 hr.	30	No injection given after 6 p.m.
4/13	2+	253	25-10-20	55	
4/14	Trace	253	30-10-25	65	Blood sugar 105 mg. at 7 p.m.
4/15	1+	217	35-10-25	70	
4/16	—	259	35- 8-27	70	Blood sugar 122 mg. at 2 p.m.
4/17	1+	306	40- 8-27	75	
4/18	..	247	40- 8-27	75	Discharged

1,887. It was necessary to increase the dosage of insulin to 40, 15 and 25 units or a total of 80 units, before the blood sugar level fell within reasonable limits, but even then the management was not satisfactory, as evidenced by appreciable glycosuria. On March 21 was instituted a regimen of divided doses with 8 units of insulin every three hours, or a total of 64 units; this produced a satisfactory decrease in blood sugar and a disappearance of sugar from the urine. On March 24 it was necessary to reduce the dosage to 7 units every three hours. On April 4 the blood sugar values obtained at intervals throughout the day and night were: 9 a. m., 183 mg.; 2 p. m., 107 mg.; 7 p. m., 131 mg.; 12 p. m., 37 mg.; 7 a. m., 44 mg., and 9 a. m., 167 mg. (meals at 7 a. m., 12 noon, and 5 p. m.). In spite of the low blood sugar value at midnight and before breakfast there were no hypo-

glycemic symptoms. However, to obviate this possibility, no injection was given at 12 p. m. from then on. With further improvement in tolerance the dosage was reduced on April 8 to 6 units every three hours except at midnight, or a total of 42 units. The patient was given this dosage until the routine of injections three times a day was resumed on April 13 with doses of 25, 10 and 20 units. This dose was insufficient and it was necessary to increase it to 40, 8 and 27, or a total of 75 units; even this dose was not entirely satisfactory, since the blood sugar value in the morning remained elevated and there was some glycosuria.

TABLE 3.—*The Values for Blood Sugar in Case 3 with Insulin in Divided Doses*

Date	Urine		Blood Sugar, Mg.		Insulin Units		Comment
	Ketone	Sugar	9 A.M.	2 P.M.	Dosage	Total	
1/26/33	—	4+	...	306	20	20	
1/27	—	1+	266	...	25-10-20	55	
1/28	—	4+	259	...	30-10-25	65	
1/29	—	3+	212	...	40-10-25	75	
1/30	—	1+	204	...	40-15-30	85	
1/31	Trace	3+	204	...	40-15-30	85	
2/ 1	—	Trace	241	...	40; 8 every 3 hr.	80	Divided dosage began at noon
2/ 2	—	—	182	...	8 every 3 hr.	64	
2/ 3	—	—	147	...	8 every 3 hr.; 7 every 3 hr.	59	
2/ 4	—	—	118	...	7 every 3 hr.; 6 every 3 hr.	51	
2/ 5	—	—	170	...	6 every 3 hr.	48	
2/ 6	—	—	167	...	6 every 3 hr.	48	
2/ 7	—	—	157	...	6 every 3 hr.	48	
2/ 8	—	—	165	...	6 every 3 hr.	48	Injection of typhoid
2/ 9	—	Trace	192	...	6 every 3 hr.	48	
2/10	—	—	211	...	6 every 3 hr.; 7 every 3 hr.	53	Infection of upper respiratory tract
2/11	—	—	159	...	7 every 3 hr.	56	
2/12	—	—	157	...	7 every 3 hr.	56	Last injection at 9 p.m.
2/13	—	—	182	...	30-8-18	56	
2/14	—	1+	...	122	30-8-18	56	
2/15	—	1+	236	104	30-5-15	50	
2/16	—	2+	236	...	35-0-22	57	
2/17	—	Trace	212	...	35-0-25	60	
2/18	Trace	2+	259	...	35-0-25	60	
2/19	Trace	Trace	35-0-30	65	
2/20	Trace	3+	192	...	35-0-30	65	
2/21	—	3+	35-0-30	65	
2/22	—	2+	189	...	35-0-35	70	
2/23	—	2+	35-0-35	70	
2/24	—	—	105	...	35-0-32	67	
2/25	35-0-32	67	Discharged

CASE 3.—LaV. L. (table 3), a youth aged 17, was admitted to the hospital on Jan. 26, 1933, with severe diabetes. He was first seen in the pediatric service over a year previously. He was discharged with instructions to follow the routine regimen, and the management of the condition was good for a time. About six months before his present admission he began to lose weight and had a recurrence of symptoms even though the dosage of insulin was increased. He was referred to the medical service for the reestablishment of his diabetic control. He was well developed and well nourished. A physical examination gave essentially negative results except for incipient bilateral cataract.

On admission the blood sugar was 306 mg. The patient was placed on a diet of protein, 70 Gm., carbohydrate, 70 Gm., and fat, 175 Gm.—calories, 2,201. Insulin in doses of 40, 15 and 30 units, or a total of 85, failed to decrease the blood sugar value taken at 9 a. m. below 200 mg. and to clear the sugar from

the urine. On February 1 he was given 8 units of insulin every three hours, or a total of 64 units. The blood sugar value promptly fell, and the sugar disappeared from the urine. On February 3 it was necessary to reduce the dose of insulin to 7 units every three hours. Management was satisfactory with this dosage until

TABLE 4.—*The Values for Blood Sugar in Case 4 with Insulin in Divided Doses*

Date	Urine		Blood Sugar, Mg.	Insulin Units		Comment
	Ketone	Sugar		Dosage	Total	
5/ 5/33	2+	3+	...	10	10	Admitted at 6 p.m.
5/ 6	2+	4+	441	10-10-20	155	Patient in coma; dextrose administered intravenously; blood sugar at 2 p.m., 200 mg.
5/ 7	2+	4+	316	24- 15-25	65	
5/ 8	Trace	3+	147	140; 8 every 3 hr.	172	Patient in coma at 5 a.m.; dextrose administered intravenously
5/ 9	Trace	—	145	8 every 3 hr.	64	
5/10	Trace	3+	124	8 every 3 hr.	56	Dose omitted at 12 p.m.
5/11	Trace	4+	231	8 every 3 hr.	64	
5/12	Trace	1+	145	8 every 3 hr.	64	
5/13	—	1+	179	8 every 3 hr.	64	
5/14	—	—	73	8 every 3 hr.	64	
5/15	—	—	...	7 every 3 hr.	56	
5/16	—	Trace	170	7 every 3 hr.	56	
5/17	—	—	82	7 every 3 hr.	56	
5/18	—	—	140	6 every 3 hr.	48	
5/19	—	—	109	6 every 3 hr.	48	Diet 75 begun at noon
5/22	—	1+	247	6 every 3 hr.	48	
5/23	—	—	90	8 every 3 hr.	64	
5/24	—	—	118	7 every 3 hr.	56	
5/26	Trace	—	140	7 every 3 hr.	56	Blood sugar 112 mg. at 2 p.m.; 129 mg. at 7 p.m.
6/ 7	—	—	142	7 every 3 hr.	56	Blood sugar 65 mg. at 2 p.m.; 36 mg. at 1 a.m.
6/ 8	—	..	129	7 every 3 hr.	56	
6/ 9	—	—	...	6 every 3 hr.	48	
6/10	—	—	87	6 every 3 hr.	48	Blood sugar 35 mg. at 6:45 a.m.; 109 mg. at 2:30 p.m.
6/11	—	—	82	6 every 3 hr.	48	Blood sugar 78 mg. at 12:20 a.m.
6/12	—	—	105	5 every 3 hr.	40	
6/13	—	—	155	4 every 3 hr.	32	
6/14	—	1+	253	4 every 3 hr.	32	
6/15	—	2+	189	4 every 3 hr.	32	
6/16	—	1+	231	4 every 3 hr.	36	4 units added at noon
6/17	—	1+	189	5 every 3 hr.	40	
6/18	—	Trace	236	5 every 3 hr.	40	
6/19	—	1+	259	5 every 3 hr.	45	5 units added at noon
6/20	—	1+	226	5 every 3 hr.	40	
6/21	Trace	1+	236	6 every 3 hr.	48	
6/22	—	—	150	6 every 3 hr.	48	
6/26	—	—	129	6 every 3 hr.	43	Blood sugar 118 mg. at 2 p.m.; 56 mg. at 12:30 a.m.
6/27	—	—	192	6 every 3 hr.	42	Last injection of divided dose given at 9 p.m.
6/28	—	1+	162	30-20	50	
6/29	Trace	4+	253	30-10-25	65	
6/30	Trace	4+	273	40- 0-30	70	Blood sugar 253 mg. at 2 p.m.
7/ 1	—	—	196	50-30	80	
7/ 2	—	—	189	50-30	80	
7/ 6	Trace	2+	241	50-10-30	90	Blood sugar 36 mg. at 2 p.m.
7/ 7	—	4+	170	50-30	80	
7/10	—	4+	159	50-30	80	Blood sugar 266 mg. at 2 p.m.
7/11	Trace	3+	162	50- 7-30	87	Blood sugar 73 mg. at 2 p.m.
7/12	—	4+	173	50- 7-30	87	Blood sugar 74 mg. at 2 p.m.; 55 mg. at 7 p.m.; 63 mg. at 4 p.m.

there developed a mild infection of the upper respiratory tract, as a result of which the blood sugar values rose; the dosage of insulin was increased to 7 units every three hours, or a total of 56 units. Regular dosage was resumed on February 13 with 30, 8 and 18 units, which was insufficient and was subsequently increased to 35 and 32, or a total of 67 units. After the return to the regular dosage, the urine showed sugar on all but the last day.

CASE 4.—E. Mc. (table 4), a youth aged 18, was admitted to the hospital on May 5, 1933. The first symptoms referable to diabetes were observed in 1927.

His first admission to the University Hospital was in 1929, at which time the diabetes was controlled with diet and insulin; he was discharged with instructions to take 20, 7 and 18 units of insulin a day. The home management of the condition was satisfactory until about a year previous to his second admission, when he had influenza. Since then the diabetes had been more severe, and he had apparently been in a state of impending coma on numerous occasions which was relieved only by food and insulin.

On admission he was placed on a diet of protein, 70 Gm., carbohydrate, 70 Gm., and fat, 175 Gm.—calories, 2,201. The patient was given 10 units of insulin before supper and before breakfast. The blood sugar content at 9 a. m. was 441 mg. Soon he showed symptoms of impending coma; a determination of carbon dioxide capacity showed an alkali reserve of 14 volumes per cent. He was immediately given 120 units of insulin and 50 Gm. of dextrose intravenously, which relieved the symptoms in a few hours. An attempt to control the diabetes on the following day with 25, 15 and 24 units of insulin failed, with a reappearance of symptoms of coma at 5 a. m. the following morning. At that time 140 units of insulin with 50 Gm. of dextrose was given, and following the relief of symptoms he was given 8 insulin units every three hours (a total of 64 units), which promptly lowered the blood sugar content and rendered the urine sugar-free, with a complete disappearance of the symptoms of acidosis. The next day because the level of the blood sugar was 124 mg. the midnight injection of 8 units was omitted. The following morning the blood sugar was 231 mg., with a 4+ reaction for sugar in the urine. Thereafter the midnight injection was included during the regimen of divided doses. Subsequently the dosage of insulin was reduced to 7, 6 and 5 and even to 4 units every three hours, but since his tolerance was not entirely stable it was occasionally necessary to increase the dosage, even after a period of satisfactory control with a lower dosage. However, for the most part, during the period of divided dosage, the blood sugar was at a reasonable level and the urine free from sugar. On May 19 the patient's diet was increased to protein, 75 Gm., carbohydrate, 75 Gm., and fat, 188 Gm.—calories, 2,358. On June 27 the patient was receiving 6 units of insulin every three hours, a total of 48 units. The next day the regular regimen was resumed, with a dosage of 30 and 20 units which was insufficient; a more satisfactory dosage was found to be 50, 7 and 30 units, or a total of 87 units, which resulted in a reasonable blood sugar value but did not keep the urine sugar-free. Blood sugar values taken at varying intervals during the day and night on several occasions were of particular interest in showing the general decrease following the ingestion of food and the low blood sugar values which obtain at night without hypoglycemic symptoms.

CASE 5.—C. M. (table 5), a woman aged 66, was admitted to the hospital late in the afternoon on Feb. 20, 1932, with acute lobar pneumonia. She had moderately severe diabetes of about two and a half years' duration. The patient had previously been admitted to the hospital on Feb. 17, 1930, at which time the diabetes was first controlled. Following discharge she managed her diabetes well until the onset of the pneumonia.

On admission, the patient's blood sugar content was 253 mg.; the temperature was 103.4 F., and the respiration was rapid and somewhat labored. There was an area of dulness at the base of the right lung, the breath sounds were suppressed, and a friction rub was present. The white blood cell count was 18,400. The diagnosis of lobar pneumonia was substantiated by roentgen examination.

The patient was given a diet of protein, 60 Gm., carbohydrate, 60 Gm., and fat, 150 Gm.—calories, 1,887; this diet was supplemented with large quantities of

fruit juice during the first few days. The patient was given 10 units of insulin on admission and 6 units at 12 p. m. and at 6 a. m. the next morning. The blood sugar content was 236 mg. at 9 a. m.; so the patient was given 12 insulin units at noon, and a dosage of 6 units every four hours was started at 4 p. m. The blood sugar level remained somewhat high, and the dosage of insulin was further increased to 7 units every three hours on the fifth day of observation, which resulted in a satisfactory blood sugar level.

The pneumonia was treated in the usual way, including the administration of oxygen by a nasal catheter and forcing of fluids. The acute symptoms rapidly subsided in three or four days, with the temperature below 101 F. On March 2 roentgen examination revealed good clearing of the pneumonic process.

TABLE 5.—*The Values for Blood Sugar in Case 5 with Insulin in Divided Doses*

Date	Urine Sugar	Blood Sugar, Mg.	Insulin Units		Comment
			Dosage	Total	
2/20/32	Trace	253	0-0-10	10	Blood sugar reading taken at 7 p.m.:
2/21	Trace	236	6-6; 6 every 4 hr.	42	Blood sugar 204 mg. at 3:30 p.m.; divided doses began at noon
2/22	—	221	6 every 4 hr.; 6 every 3 hr.	48	Changed to 6 units every 3 hr. at noon
2/23	—	173	6 every 3 hr.	48	
2/24	—	236	6 every 3 hr.; 7 every 3 hr.	53	Changed to 7 units at noon
2/25	—	173	7 every 3 hr.	56	
2/26	—	150	7 every 3 hr.	56	
2/27	—	124	7 every 3 hr.; 6 every 3 hr.	51	
2/28	—	104	6 every 3 hr.; 6 every 4 hr.	42	
2/29	—	118	6 every 4 hr.; 5 every 4 hr.	32	
3/ 1	—	131	5 every 4 hr.; 10	25	Divided dosage ended at noon
3/ 2	—	79	20-0-7	27	
3/ 3	—	112	15	15	
3/ 4	—	131	15	15	
4/ 5	—	102	15	15	
3/ 6	—	105	12	12	
3/ 7	—	105	9	9	
3/ 8	—	157	7	7	
3/ 9	—	147	7	7	
3/10	—	110	7	7	
3/11	—	105	7	7	
3/12	..	182	0	0	Discharged

As the pneumonic condition improved there was a marked improvement in the diabetes, necessitating a rapid reduction in the dosage of insulin. On March 1 the patient was receiving 5 units of insulin every four hours, or a total of 30 units. The following day regular dosage was resumed with 20 and 7 units; the blood sugar value in the morning was 79 mg. The dose of insulin was reduced to 15 units before breakfast only. The rapid improvement continued with the disappearance of the pneumonia, and the patient was discharged on March 12 without further treatment with insulin.

CASE 6.—L. C. (table 6), a woman aged 22, was admitted to the hospital on Feb. 2, 1932, with severe diabetes of about five years' duration. She complained of severe pain and tenderness of the right shoulder, the right hip and the left knee. The Wassermann reaction of the blood was positive; she had had leukorrhea for over a year, but no gonococci could be demonstrated in the smears. Roent-

genologically the right hip showed definite destruction of the intra-articular cartilages suggestive of infectious arthritis.

Treatment of the arthritis consisted primarily of traction and immobilization of the legs in a cast. The patient had a septic temperature, which ranged between 99 and 102 F.; the temperature slowly dropped and remained practically normal after March 18. The patient was placed in a double leg spica cast on February 13.

TABLE 6.—*The Values for Blood Sugar in Case 6 with Insulin in Divided Doses*

Date	Urine Sugar	Blood Sugar, Mg.	Insulin Units		Comment
			Dosage	Total	
2/ 2/32	...	170	8	8	
2/ 3	4+	349	15-15-20	50	
2/ 4	...	289	30-10-20	60	
2/ 5	...	316	30-10-20	72	6 units every 3 hr. began at 9 p.m.
2/ 6	...	217	6 every 3 hr.	48	
2/ 7	...	241	6 every 3 hr.; 7 every 3 hr.	53	
2/ 8	...	155	7 every 3 hr.	56	
2/ 9	...	192	7 every 3 hr.	56	
2/10	...	179	7 every 3 hr.	56	
2/12	0	131	7 every 3 hr.	56	
2/13	0	189	7 every 3 hr.	56	Blood sugar, 212 mg. at 2 p.m.
2/14	Trace	241	7 every 3 hr.	56	
2/15	0	189	7 every 3 hr.	56	
2/16	0	129	7 every 3 hr.; 6 every 3 hr.	51	
2/18	0	96	6 every 3 hr.; 6 every 4 hr.	42	
2/20	...	120	6 every 4 hr.	36	
2/21	...	95	6 every 4 hr.; 5 every 4 hr.	33	
2/22	...	118	5 every 4 hr.; 6 every 6 hr.	27	
2/23	...	196	6 every 6 hr.	24	
2/25	...	176	6 every 6 hr.	24	
2/27	0	133	6 every 6 hr.	24	
2/29	...	165	6 every 6 hr.	24	
3/ 1	6 every 6 hr.	24	Transferred to orthopedic service
3/ 3	...	186	6 every 6 hr.	24	
3/ 9	...	186	6 every 6 hr.	24	
3/21	...	72	6 every 6 hr.	24	Blood sugar reading taken at 2 p.m.
3/23	6 every 6 hr.; 5 every 6 hr.	22	Blood sugar reading taken at 2 p.m.
3/30	...	204	5 every 6 hr.	20	Blood sugar reading taken at 2 p.m.
3/31	...	124	5 every 6 hr.	20	
4/11	...	84	5 every 6 hr.	20	
4/12	5 every 6 hr.; 4 every 6 hr.	18	
4/27	...	167	4 every 6 hr.	16	
5/10	0	...	4 every 6 hr.	16	Transferred to the medical service
5/11	0	98	10	10	
5/12	0	145	7	7	
5/13	0	145	7	7	
5/14	0	192	7	7	
5/16	0	192	7	7	Discharged, receiving 10 units

Shortly afterward a pressure sore appeared, and she was transferred to the orthopedic service for treatment. The pressure necrosis responded to treatment slowly. She had received definite relief from the cast and on its removal was able to make some motion without pain. Antisymphilitic treatment was started. She was returned to the medical service on May 10 for final control of the diabetes before discharge.

The patient had been taking about 120 units of insulin daily previous to admission to the hospital. On admission the blood sugar level was 170 mg. She was placed on a diet of protein, 60 Gm., carbohydrate, 60 Gm., and fat, 150 Gm.—

calories, 1,887. Insulin in doses of 30, 10 and 20 units, or a total of 60 units, failed to control the diabetes, for the blood sugar remained over 300 mg. On February 5, the fourth day of observation, the patient was given a dosage of 6 insulin units every three hours, which was increased to 7 units every three hours, or a total of 56 units. With this dosage management was satisfactorily established, as evidenced by the postabsorptive blood sugar content after two hours. As the acute stage of the infection subsided, the dosage of insulin was progressively reduced to 4 units every six hours on April 12. On May 11 the regular regimen was resumed, with 10 units before breakfast only. The dose was reduced to 7 units before breakfast, but that was a little too low, and the patient was discharged on May 16 receiving 10 units a day.

CASE 7.—C. J. (table 7), a youth aged 20, was admitted to the hospital on Aug. 30, 1933. He had severe diabetes of about five years' duration and had had

TABLE 7.—*The Values for Blood Sugar in Case 7 with Insulin in Divided Doses*

Date	Urine		Blood Sugar, Mg.	Insulin Units		Comment
	Ketone	Sugar		Dosage	Total	
8/30/33	3+	4+	480	25	25	Blood sugar reading taken at 3 p.m.
8/31	Trace	4+	362	25-30-25	80	
9/ 1	Trace	4+	372	30-20; 8 every 3 hr.	74	Divided doses begun at 3 p.m.; injection omitted at 12 p.m.
9/ 2	Trace	4+	372	8 every 3 hr.; 20; 10 every 3 hr.	84	Injection omitted at 12 p.m.
9/ 3	0	2+	372	10 every 3 hr.; 25; 8 every 2 hr.	103	Injection omitted at 12 p.m.
9/ 4	0	1+	316	8 every 2 hr.; 10 every 2 hr.	100	Injection omitted at 12 p.m.
9/ 5	0	0	236	10 every 2 hr.	110	Injection omitted at 12 p.m.
9/ 6	0	0	179	10 every 2 hr.; 9 every 2 hr.	104	Injection omitted at 12 p.m.
9/ 7	0	0	273	9 every 2 hr.	99	Injection omitted at 12 p.m.
9/ 8	0	0	186	9 every 2 hr.	99	Injection omitted at 12 p.m.
9/10	0	0	170	9 every 2 hr.	99	Injection omitted at 12 p.m.
9/12	0	0	155	9 every 2 hr.	99	Injection omitted at 12 p.m.
9/14	0	0	147	9 every 2 hr.	99	Injection omitted at 12 p.m.
9/16	0	0	60	9 every 2 hr.; 8 every 2 hr.	77	Last injection of divided doses at 6 p.m.
9/17	0	0	204	40-15-30	85	
9/18	0	0	182	40-15-30	85	
9/19	0	0	266	40-15-30	85	
9/20	0	0	204	45-12-30	87	Discharged

a number of previous admissions to the hospital. Twenty-four hours after the present admission, he was operated on, and nearly 500 cc. of purulent fluid was drained from a perinephric abscess. *Staphylococcus aureus* was isolated from the purulent fluid.

The patient was placed on a diet of protein, 70 Gm., carbohydrate, 70 Gm., and fat, 175 Gm.—calories, 2,201. The blood sugar level on admission was 480 mg. at 3 p. m. He was given 25 units of insulin before supper and before breakfast the following morning; the blood sugar level at 9 a. m. was 362 mg. He was operated on that afternoon, following the injection of 30 units of insulin and the ingestion of 50 Gm. of dextrose in orange juice. (It is the routine preoperative procedure to give the patient 50 Gm. of dextrose either by mouth or intravenously with about 10 extra units of insulin about two hours preceding the operation.) Postoperatively 30, 20 and 25 units of insulin failed to control the diabetes. Accordingly, a regimen of divided doses was instituted, with 8 units of insulin every three hours except at 12 p. m., a dosage which was not sufficient. The dosage was increased to 8 units every two hours except at midnight, and

finally to 10 units every two hours except at midnight. This dosage reduced the blood sugar to a reasonable value with the disappearance of sugar from the urine. In the course of two days it was necessary to reduce the dosage to 9 units every two hours except at midnight. The postoperative course was satisfactory for such an extensive lesion. On the day preceding the resumption of the regular dosage, the requirement of insulin was reduced from 99 to 88 units a day. The patient was discharged on September 20 with instructions to take 45, 12 and 30 units, or a total of 87 units; the blood sugar value was somewhat elevated, but the urine was free from sugar.

R. G. Snyder, M.S., determined the blood sugar level of the patients in the eleven experimental cases in 1929-1930.

INFLUENCE OF DI-NITROPHENOL ON CARBOHYDRATE METABOLISM

MAX WISHNOFSKY, M.D.

ARTHUR P. KANE, M.D.

EDMUND L. SHLEVIN, M.D.

AND

CHARLES S. BYRON, M.D.

BROOKLYN

It is well known that a disturbance in carbohydrate metabolism occurs in conditions in which there is an increase in heat production.

In reference to this subject Wilder ¹ made the following statements:

The exophthalmic goiter syndrome reduces the ability of the diabetic patient to utilize carbohydrate; decreases the efficiency of the unit of insulin; increases the danger of sudden onset of diabetic coma, and the control of this syndrome by the administration of iodine markedly improves the carbohydrate tolerance. . . . A mild and possibly inconspicuous or latent spark of diabetes may be fanned into flame by hyperthyroidism. . . . When thyroid is given to patients with diabetes, a marked intensification of glycosuria occurs and persists some time after the drug is discontinued. . . . An improvement in tolerance [in diabetes mellitus] has occurred within a week or ten days after thyroidectomy in almost every case. . . . Boothby and I have pointed out that the influence of heavy protein dietaries in diabetes is much like that of hyperthyroidism in that such diets stimulate the metabolism by their high specific dynamic actions and that as the metabolic rate rises the tolerance falls. Fever, as is well known, elevates the metabolic rate and simultaneously depresses sugar tolerance. . . . The action of drugs with a calorogenic influence has thus far not been studied except in the case of thyroxin and epinephrine, both of which lower tolerance. In general it appears that all those measures or conditions which stimulate the general metabolism have a depressing action on the tolerance of the diabetic patient. . . . I am aware of only one exception to this generalization, namely exercise. . . . The higher the metabolic rate the greater is the demand for insulin, even though the total amount of sugar to be utilized in a given time remains constant. The lower the metabolic rate the less the amount of insulin required to do the same work in the same time.

This study was aided by a grant from the Committee on Scientific Research of the American Medical Association.

From the Medical Service of Dr. S. R. Blatteis, Divisions of Diabetes and Metabolism, and the Department of Pathology of the Jewish Hospital, Brooklyn.

1. Wilder, R. M.: Hyperthyroidism, Myxedema and Diabetes, Arch. Int. Med. 38:736 (Dec.) 1926.

Fitz² also suggested that the unfavorable influence of hyperthyroidism may be due more to the resulting increased rate of total metabolism than to any direct effect of the thyroid gland on carbohydrate metabolism.

Fever is usually associated with infection, so that it is difficult to determine to what extent the former alone is responsible for the disturbance in carbohydrate metabolism. Walinski,³ in studies on uncomplicated elevation of the body temperature, found a rise in the blood sugar level which could be explained by the concentration of the blood.

It has been known since the latter half of the last century that exercise improves the tolerance of the diabetic patient for carbohydrates. Allen, Stillman and Fitz⁴ stressed this action. More recently Gerl and Hoffman⁵ have found that exercise reduces glycemia and the requirement for insulin. This action occurs in mild and moderately severe but not in severe cases of diabetes. Lawrence⁶ also observed that exercise markedly enhances the blood sugar-lowering effect of insulin and drew the distinction between mild and severe cases. Grafe and Salomon⁷ and Richardson and Levine⁸ found that in diabetes exercise causes a depression of the respiratory quotient indicating that proportionately fat is undergoing greater oxidation. There is, however, an absolute increase in the amount of carbohydrate oxidized. This is true for patients with mild but not for those with severe diabetes.

Di-nitrophenol causes an increase in oxidative metabolism by direct stimulation of the cell. This action occurs independently of the central nervous system or of muscular contraction and is not prevented by ergotamine or by adrenalectomy or thyroidectomy.⁹ It was thought of interest, therefore, to study its influence on carbohydrate metabolism both in normal persons and in patients suffering from diabetes mellitus.

2. Fitz, R.: Relation of Hyperthyroidism to Diabetes, *Arch. Int. Med.* **27**:305 (March) 1921.

3. Walinski, F.: Ueber das Verhalten des Blutzuckers und Schweisszuckers bei künstlicher Hyperthermie, *Deutsche med. Wchnschr.* **58**:1475, 1932.

4. Allen, F. M.; Stillman, E., and Fitz, R.: Total Dietary Regulation in Treatment of Diabetes Mellitus, Monogr. 1, New York, Rockefeller Institute for Medical Research, 1919, p. 495.

5. Gerl, A., and Hoffman, H.: Muskularbeit und Insulinbedarf beim Diabetes, *Klin. Wchnschr.* **7**:59, 1928.

6. Lawrence, R. D.: Effect of Exercise on Insulin Action in Diabetes, *Brit. M. J.* **1**:648, 1926.

7. Grafe, E., and Salomon, H.: Ueber den Einfluss der Muskularbeit auf die Intensität der Zuckerverbrennung beim Diabetiker, *Deutsches Arch. f. klin. Med.* **139**:369, 1922.

8. Richardson, H. B., and Levine, S. F.: Exercise and Respiratory Quotient in Diabetes, *J. Biol. Chem.* **66**:161, 1925.

9. Tainter, M. L., and Cutting, W. C.: Febrile, Respiratory and Some Other Actions of Dinitrophenol, *J. Pharmacol. & Exper. Therap.* **48**:410, 1933.

METHOD OF STUDY

In normal persons the influence of di-nitrophenol on the concentration of the blood sugar was examined both during fasting and after the ingestion of dextrose. The study was performed on ten patients of whom nine suffered from trivial complaints. One patient (case 2) had juvenile hypopituitarism.

In the morning, after the patients had fasted for fourteen hours, the basal metabolism was determined with the Sanborn apparatus (indirect calorimetry by the closed method). A specimen of venous blood was then taken, and the patients

TABLE 1.—*The Concentration of Dextrose in the Blood of Normal Persons During Fasting and After the Ingestion of 100 Gm. of Dextrose Before and After the Administration of Di-nitrophenol*

Case	Blood Sugar*							
	During Fasting		Forty-Five Min. Post Cibus		Two Hours Post Cibus		Basal Metabolism	
	Period of Control	After Di nitro phenol	Period of Control	After Di nitro phenol	Period of Control	After Di nitro phenol	Period of Control	After Di nitro phenol
1	93	102	150	205	121	132	+11	+28
2	87	117	88	123	104	122	+5	+42
3	100	123	163	205	117	140	+5	+36
4.	98	125	120	180	102	127	+4	+34
5.	114	133	176	230	178	182	+4	+17
6	120	141	200	214	164	163	+6	+48
7..	101	120	133	168	114	136	+5	+52
8.	117	121	132	115	140	166	+6	+24
9.	99	107	135	163	117	134	+10	+93
10..	98	115	163	185	121	141	+1	+28
Means.	102.7	120.4	146.0	178.8	127.8	144.5		
Difference between means†	+17.7		+32.8		+16.7			
n..	9		9		9			
t	6.65		4.51		5.79			
p..	<0.01		<0.01		<0.01			

* Milligrams per hundred cubic centimeters of blood.

† The sign of the difference is taken as plus when the value is greater after, and as minus when the value is greater before, the administration of di-nitrophenol.

were given 100 Gm. of dextrose in sufficient aqueous solution to constitute a total volume of 500 cc. Specimens of blood were then taken forty-five minutes and two hours after the administration of the dextrose. The sugar content of the blood was determined by the Folin-Wu method. For six days following this procedure the patients took 75 mg. of alpha-di-nitrophenol orally, three times a day after meals. No changes were made in their diets. On the seventh day, early in the morning, on an empty stomach, they took 75 mg. of alpha-di-nitrophenol. One hour later the basal metabolism and the blood sugar level, both before and after the administration of dextrose, were studied exactly as on the control day, before the administration of the alpha-di-nitrophenol.

The method of study used for diabetic patients was practically identical with that followed for the normal persons. In the interval between the tests the patients received their customary diets. Those who had been taking insulin continued to do so. Seventy-five instead of 100 Gm. of dextrose was given. The sodium salt of di-nitrophenol was given in a dose of 100 mg. three times a day after meals.

The amount of sugar in the urine was also determined. The urine was collected for exactly two hours after the ingestion of the dextrose, and its sugar content was determined by Benedict's method.

ANALYSIS OF RESULTS

Results in Normal Persons.—Table 1 shows the concentration of the blood sugar during fasting and after the administration of di-nitrophenol. On inspection it is evident that there is a significant difference, the values after the administration of di-nitrophenol being uniformly higher. The impression is confirmed when the results are analyzed statistically.¹⁰ No attempt was made to correlate the degree of rise in the concentration of the blood sugar with the rise in basal metabolism because of the small size of the series.

There is still a controversy as to whether the blood sugar level during fasting is raised in hyperthyroidism, but in at least 60 per cent of the cases the curve for the blood sugar is elevated after the administration of dextrose. Sanger and Hun¹¹ ascribed the heightened curve for the blood sugar to defective storage of glycogen in the liver. Richardson, Levine and Du Bois,¹² however, produced evidence against the theory that there is any defect in glycogenesis. As mentioned, Wilder¹ attributed the hyperglycemia and the glycosuria to the elevated metab-

10. The method of analysis used was that developed by R. A. Fisher (Statistical Methods for Research Workers, ed. 3, London, Oliver and Boyd, 1930, p. 104). As an example one may consider the results for the blood sugar level during fasting. The mean difference in this instance is + 17.7, the plus sign indicating that the value is higher after the administration of di-nitrophenol. The value of t is derived as follows:

$$\frac{s^2}{n'} = \frac{1}{n'(n'-1)} \sum (x - \bar{x})^2 = 7.09$$

$$t = \frac{\bar{x} \sqrt{n'}}{s} = 6.65$$

If the table in Fisher's book is consulted, it is found that if n equals 9, when n equals $n' - 1$, n' being the number of cases of the series, the highest value recorded for t is 3.250, this value for t occurring once in a hundred cases. The fact that the value for t found at the fasting level is much higher than this is decidedly significant. The same holds true for the blood sugar at the forty-five minute level (t equals 4.51) and at the two hour level (t equals 5.79). For all these values of t , p is far less than 0.01. The conventional limit of significance of p is 0.05.

11. Sanger, B. J., and Hun, E. G.: The Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. 30:397 (Sept.) 1922.

12. Richardson, H. B.; Levine, S. Z., and Du Bois, E. F.: Storage of Glycogen in Exophthalmic Goitre, J. Biol. Chem. 67:737, 1926.

olism. Some authors contend that thyroid extract has a toxic action on the islet tissue of the pancreas.¹³

Epinephrine causes glycogenolysis and inhibits glycogenesis in the liver and probably also in the muscles. This action is probably mediated through the sympathetic nervous system.¹⁴

Exercise produces an initial hyperglycemia followed by hypoglycemia if the exercise is exhausting and prolonged.¹⁵

Experimental work has been done by Hall and his co-workers¹⁶ on the influence of huge doses of di-nitrophenol (from 20 to 30 mg. per kilogram of body weight) on the blood sugar level during fasting in dogs. These authors found that the level was elevated 70 mg. per hundred cubic centimeters of blood. In the liver and in skeletal muscle the glycogen content fell. Examination of the liver post mortem did not reveal any anatomic lesions; nor did studies of the hepatic function reveal any changes. They considered the rise in blood sugar concentration as an indication that glycogenolysis was occurring actively.

Our experiments show that an elevation of the blood sugar level also occurs after the ingestion of dextrose. Forty-five minutes after the ingestion of an adequate amount of dextrose the tissues are flooded with dextrose and the predominant process in the liver is glycogenesis. There is no need for active glycogenolysis. The contention of Hall and his co-workers¹⁶ is, therefore, untenable. We are at a loss to explain the mechanism by which an increase in heat production causes an elevation in the concentration of blood sugar both during fasting and after the ingestion of dextrose. It is important to note that the rise in the blood sugar level which occurs in hyperthyroidism, hypersuprarenalism and exercise must be ascribed in part to the increase in oxidative metabolism.

Results in Patients with Diabetes Mellitus.—As discussed in the review of the literature, the prevailing opinion is that all measures,

13. Shpiner, L. B.: Increased Metabolism Only One Factor in Production and Maintenance of Hyperglycemia and Glycosuria in Experimental Hyperthyroidism, *Am. J. Physiol.* **92**:672, 1930.

14. Sollmann, T.: *Manual of Pharmacology*, ed. 4, Philadelphia, W. B. Saunders Company, 1932, p. 450.

15. Levine, S. A.; Gordon, B., and Derick, C. L.: Some Changes in the Chemical Constituents of the Blood Following a Marathon Race, *J. A. M. A.* **82**:1778 (May 31) 1924. Rakestraw, N. W.: Effect of Muscular Exercise upon Certain Common Blood Constituents, *J. Biol. Chem.* **47**:565, 1921. Rakestraw, N. W.; Barley, C. V., and Hahn, Y. D.: Further Changes in Blood Constituents Following Strenuous Muscular Exercise, *J. Biol. Chem.* **56**:121, 1923. Bürger, M.: Die Wirkung der Arbeit auf den Zuckergehalt des menschlichen Blutes, *Ztschr. f. d. ges. exper. Med.* **5**:125, 1916.

16. Hall, V. E., et al.: Carbohydrate Metabolism, Respiration, and Circulation in Animals with Basal Metabolism Heightened by Dinitrophenol, *Am. J. Physiol.* **106**:432, 1933.

except exercise, which stimulate the general metabolism have a depressing action on the tolerance of the diabetic patient for carbohydrates.¹⁷ Di-nitrophenol is an ideal substance with which to test the validity of this conception, for, in the words of Hall and his associates: ¹⁶ "Dinitrophenol is well adapted to the experimental study of the various responses of the organism to conditions of accelerated tissue metabolism."

The only work on this subject has been done by Tainter, Boyes and De Eds ¹⁸ on dogs rendered totally diabetic by pancreatectomy. The scope of their work is limited, however, for they employed only lethal doses. Their conclusions are as follows: 1. Di-nitrophenol kills pancreatectomized dogs before the usual febrile and respiratory responses to the drug are fully developed. 2. This increased toxicity is conditioned by a lack of insulin since it may be partially abrogated by adequate administration of insulin. 3. There is no significant change in the acid-base equilibrium. 4. Di-nitrophenol should be used cautiously in diabetic patients because of the possibility of increased toxicity.

As an index of the effect of di-nitrophenol on the carbohydrate tolerance in diabetes we used the following criteria: (1) its effect on the blood sugar level during fasting; (2) its effect on the concentration of the blood, and (3) the excretion of dextrose in the urine after the ingestion of 75 Gm. of dextrose.

It was also necessary to take into account the possibility that the influence of the drug might be different in mild and in severe cases, because, as has been mentioned, such a difference has been observed following exercise. Purely arbitrarily, patients for whom the blood sugar value during fasting was below 250 mg. per hundred cubic centimeters were considered as having mild or moderately severe diabetes, and those for whom the value was above this level, as having severe diabetes.

In tables 2 and 3 is shown the effect of di-nitrophenol in diabetes mellitus on (1) the concentration of dextrose in the blood during fasting and (2) the concentration of dextrose in the blood and (3) the amount of dextrose in the urine after the ingestion of 75 Gm. of dextrose. A statistical analysis failed to reveal any significance in the mean values for the blood sugar before and after the administration of di-nitrophenol. This was true regardless of the severity of the diabetes. As far as the

17. Wilder.¹ Fitz.² In response to a query as to the use of di-nitrophenol in diabetes mellitus, the editor of *The Journal of the American Medical Association* answered in part as follows: "There are even stronger reasons to oppose the use of dinitrophenol when the patient has diabetes. The tolerance in diabetes is depressed by measures of all kinds that elevate the basal metabolic rate, and this is the action of dinitrophenol" (*Dinitrophenol Contraindicated in Diabetes, Queries and Minor Notes*, J. A. M. A. **102**:2135 [June 23] 1934).

18. Tainter, M. L.; Boyes, J. H., and DeEds, F.: *Actions of Dinitrophenol in Diabetic Dogs*, *Arch. internat. de pharmacodyn. et de therap.* **45**:235, 1933.

TABLE 2.—*The Influence of Di-nitrophenol in Mild and Moderately Severe Cases of Diabetes on the Concentration of Dextrose in the Blood Before and After the Ingestion of 75 Gm. of Dextrose and on the Quantity of Dextrose in the Urine After the Ingestion of 75 Gm. of Dextrose*

Case	Blood Sugar*						Urine Sugar† From		Basal Metabolism	
	During Fasting		Forty-Five Minutes Post Cibum		Two Hours Post Cibum		0 to 2 Hours Post Cibum			
	Period of Control	After Di-nitro-phenol	Period of Control	After Di-nitro-phenol	Period of Control	After Di-nitro-phenol	Period of Control	After Di-nitro-phenol	Period of Control	After Di-nitro-phenol
1.....	242	152	400	328	428	336	24.4	18.0	+25	+82
2.....	250	196	328	308	364	384	11.2	2.6	+1	+33
3.....	150	138	250	240	300	250	5.4	0.9	+5	+42
4.....	124	240	364	360	422	460	18.4	9.0	+2	+38
5.....	176	146	256	242	231	182	4.4	1.5	+7	+31
6.....	168	228	300	352	378	374	3.2	3.4	+4	+49
7.....	234	220	356	328	19.6	16.4	+25	+62
8.....	238	230	410	405	374	508	1.3	1.6	+4	+44
9.....	222	202	378	300	408	428	9.0	4.8	+4	+61
10.....	98	126	224	224	264	296	0.9	0.3	0	+21
11.....	224	244	332	360	364	328	5.9	7.1	+36	+81
Means.....	193.3	192.9	327.1	313.4	359.3	354.6	9.43	5.96		
Difference between means‡	—0.4		—13.7		—4.7		—3.47			
n.....	10		10		9		10			
t.....	0.217		1.20		0.190		3.18			
p.....	>0.9		0.2 to 0.3		0.8 to 0.9		0.01			

* In milligrams per hundred cubic centimeters of blood.

† In grams.

‡ The sign of the difference is taken as plus when the value is greater after, and as minus when the value is greater before, the administration of di-nitrophenol.

TABLE 3.—*The Influence of Di-nitrophenol in Severe Cases of Diabetes on the Concentration of Dextrose in the Blood Before and After the Ingestion of 75 Gm. of Dextrose and on the Quantity of Dextrose in the Urine After the Ingestion of 75 Gm. of Dextrose*

Case	Blood Sugar*						Urine Sugar† From		Basal Metabolism	
	During Fasting		Forty-Five Minutes Post Cibum		Two Hours Post Cibum		0 to 2 Hours Post Cibum			
	Period of Control	After Di-nitro-phenol	Period of Control	After Di-nitro-phenol	Period of Control	After Di-nitro-phenol	Period of Control	After Di-nitro-phenol	Period of Control	After Di-nitro-phenol
1.....	374	476	526	600	566	750	25.1	15.9	+22	+69
2.....	272	230	410	422	556	500	12.4	4.3	+6	+39
3.....	288	302	460	404	516	516	11.8	10.3	+20	+32
4.....	284	272	454	400	428	508	21.9	16.1	+7	+19
5.....	283	332	400	434	335	526	16.0	4.6	+14	+25
6.....	252	150	428	273	440	268	11.8	4.5	+23	+44
7.....	340	272	536	416	680	536	14.9	12.3	+4	+28
8.....	364	248	566	394	508	484	13.4	5.9	+10	+30
9.....	266	230	384	348	500	411	17.1	11.5	+1	+35
Means.....	302.5	279.1	462.7	410.1	508.8	499.9	16.04	9.49		
Difference between means‡	—23.4		—52.6		—8.9		—6.53			
n.....	8		8		8		8			
t.....	0.995		1.86		0.204		6.25			
p.....	0.3 to 0.4		0.1		0.8 to 0.9		Far < 0.01			

* In milligrams per hundred cubic centimeters of blood.

† In grams.

‡ The sign of the difference is taken as plus when the value is greater after, and as minus when the value is greater before, the administration of di-nitrophenol.

excretion of dextrose in the urine is concerned, however, a significant decrease in glycosuria was observed following the ingestion of the drug, and this was more pronounced in the severe cases. Di-nitrophenol, even in lethal doses, does not produce anatomic changes in the kidneys. Since the curves for the blood sugar before and after the administration of the drug are identical, one must conclude that an elevation of the renal threshold for dextrose is produced.

The findings in these experiments offer a direct proof that an increase in oxidative metabolism does not cause a depreciation of tolerance for carbohydrates in diabetes mellitus. The decrease in tolerance which occurs in diabetes mellitus associated with hyperthyroidism and other conditions in which the heat production is increased must be ascribed to other factors.

All the patients took di-nitrophenol for one week only. No untoward reactions were observed in the normal persons. Tainter stated that the drug should be administered cautiously to diabetic patients because severe reactions are likely to occur. That has not been our experience. Of the twenty patients who used di-nitrophenol untoward symptoms developed in only one. That patient suffered from diarrhea, and whether di-nitrophenol was the cause is conjectural.

SUMMARY AND CONCLUSIONS

In normal persons, di-nitrophenol causes a significant increase in the concentration of the blood sugar both during fasting and after the ingestion of dextrose. In the present state of our knowledge the causative mechanism cannot be determined. The elevation of the blood sugar level in hyperthyroidism, hypersuprarenalism and other conditions in which there is an augmentation in heat production must in part be attributed to the increase in oxidative metabolism.

Di-nitrophenol does not cause any significant change in the concentration of the blood sugar in diabetes mellitus, either during fasting or after the ingestion of dextrose. There is, however, a decided reduction in glycosuria after the administration of dextrose, which is to be explained on the basis of an elevation of the renal threshold for dextrose. These findings offer direct proof that an increase in oxidative metabolism does not cause a depreciation in tolerance for carbohydrates in diabetes mellitus. The decrease in tolerance which occurs in diabetes mellitus associated with hyperthyroidism and other conditions in which there is an increase in heat production must be ascribed to other factors.

The findings reported here are not to be taken as a brief for the use of di-nitrophenol. The sole purpose of this work was to study the influence of increased heat production on carbohydrate metabolism.

Dr. A. S. Wiener made the statistical analysis of the data.

Progress in Internal Medicine

INFECTIOUS DISEASES

REVIEW OF THE CURRENT LITERATURE

HOBART A. REIMANN, M.D.

MINNEAPOLIS

An enormous number of papers dealing with infectious diseases have appeared during the current year. Considerable progress has been made in the more common diseases, especially in pneumonia and influenza, and in a number of rarer diseases, such as encephalitis, tetanus and psittacosis. Many new features of academic interest have developed in the field of bacteriology, especially in regard to the classification of hemolytic streptococci and to certain of its biologic reactions and in the general field of microbic dissociation.

Pneumonia.—The rational practice of regarding pneumonia from an etiologic point of view instead of from an anatomic one has gained much ground. The terms lobar pneumonia and bronchopneumonia are no longer considered satisfactory and must be qualified by terms indicating the causative organism. Even the restricted clinico-anatomic syndrome recognized as pneumococcic lobar pneumonia has been shown to be not a single disease but a group of specific infections, each caused by a different type of pneumococcus, with many clinical and pathologic features in common. The newer ideas in regard to the etiologic classification and treatment are summarized by Finland¹ and Bullowa.^{1a} Cooper's work in separating pneumococci heretofore placed in group IV into twenty-nine separate types, making in all thirty-two fixed types, has been confirmed on all sides.

An interesting study by Gautier² deals with pneumonia as it occurs in the tropics. The similarity in the incidence of the various types of pneumococci causing pneumonia in such widely separated places as Japan, Australia, India, Ecuador, the Transvaal and Germany is remark-

From the Department of Medicine, the University of Minnesota Hospital.

1. Finland, M.: The Use of Serum in the Treatment of Pneumonia, *M. Clin. North America* **18**:1093, 1935.

1a. Bullowa, J. G. M.: Pneumonia Due to *Pneumococcus* Type XIV (Cooper) and Its Treatment with Specific Serum, *J. Clin. Investigation* **14**:373 (July) 1935.

2. Gautier, R.: Tropical Pneumonia, *Quart. Bull. Health Organ., League of Nations* **1**:64 (March) 1932.

able. His study further confirms the constancy and world-wide distribution of the types of *Pneumococcus*. The general mortality rate for pneumonia of all kinds, according to statistics from world-wide sources, is also remarkably constant, averaging between 30 and 40 per cent. The most frequent types of *Pneumococcus* encountered in cases of pneumonia are I, II, III, VIII, VII and V in approximately that order. These six types together are responsible for about 80 per cent of the cases of pneumococcic pneumonia.¹

According to Finland and Sutliff,³ about one fifth of pulmonary infections due to type III and one third of those due to type VIII are to be regarded not as typical lobar pneumonia but as atypical or bronchopneumonia. Infections due to types III and VIII are less often "primary" but usually complicate illness due to other causes, such as autogenous infections. It has also been shown that occasionally several types of *Pneumococcus* may be encountered in the same patient;⁴ in such a case (a) one type may be the effective invader and the other incidental, (b) two types may concurrently produce infection or (c) different types may cause consecutive infections. Finland and Winkler,⁵ corroborating the results of older studies, show that recurrence of pneumonia took place in 16.5 per cent of 1,000 cases. Subsequent attacks were due to the same type or to different types of *Pneumococcus*. Several papers, including publications from Germany and England,⁶ further attest to the value of type I antiserum when properly administered.

Cohn and Lewis⁷ restudied the problem of digitalis therapy in pneumonia. They concluded that: (a) the drug did not influence the course of events in the disease, (b) in the cases considered its action is beneficial when auricular fibrillation or flutter occurs, (c) digitalis may precipitate the occurrence of auricular fibrillation, and (d) heart block occurred during pneumonia in some cases when a sufficient amount of digitalis was given to bring it about.

The use of artificial pneumothorax in the treatment of lobar pneumonia has recently attracted wide attention. Favorable results are

3. Finland, M., and Sutliff, W. D.: Infections with *Pneumococcus* Type III and Type VIII, *Arch. Int. Med.* **53**:481 (April) 1934.

4. Finland, M.: The Significance of Mixed Infections in *Pneumococcic* Pneumonia, *J. A. M. A.* **103**:1681 (Dec. 1) 1934.

5. Finland, M., and Winkler, A. W.: Recurrences in *Pneumococcus* Pneumonia, *Am. J. M. Sc.* **188**:309 (Sept.) 1934.

6. Sutliff, W. D., and Finland, M.: Type I *Pneumococcic* Infections with Especial Reference to Specific Serum Treatment, *New England J. Med.* **210**:237 (Feb. 1) 1934; The Serum Treatment of Lobar Pneumonia: A Report of the Committee of the National Research Council, *Brit. M. J.* **1**:241 (Feb. 10) 1934.

7. Cohn, A. E., and Lewis, W. H.: Lobar Pneumonia and Digitalis, *Am. J. M. Sc.* **189**:457 (April) 1935.

reported by Blake and his co-workers⁸ and by Behrend and Cowper.⁹ The results of Hines and Bennett¹⁰ were not as striking; an artificial crisis was induced in 4 of 12 patients, and 4 died. The best results are said to be obtained if the lung is collapsed before the third day of illness, if no adhesions are present and if only one lung is involved. Although too few patients have as yet been treated to enable one to evaluate the method with certainty, the procedure seems to induce crisis in certain instances. It is claimed that the inflamed lung is set at rest and that pleuritic pain, if present, is abolished.

Questions occurring naturally to most observers are raised in the discussion of Blake's paper⁸: (a) How can a consolidated lung be collapsed? (b) How can the presence of fibrous adhesions be determined before introducing air? (c) Do not further pressure in the thorax and the collapse of the adjacent uninvolved portion of the lung dangerously increase the anoxemia already present? The replies in effect are as follows: (a) During the early period of consolidation the lungs are still compressible, as shown by roentgenographic studies. (b) The presence of adhesions can be determined after the first and second attempts to introduce air. (c) A deliberate attempt is made to collapse all the lobes on the side involved, and no harmful effects from the reduced amount of pulmonary tissue have as yet been observed. The method is still in the experimental stage. If it is proved safe and effective the treatment of pneumonia will be simplified, especially that of pneumonia of the type for which no specific therapy exists.

A recent paper by Avery and his associates¹¹ reports the effectiveness of a bacterial enzyme which specifically decomposes the polysaccharide in the capsule of *Pneumococcus* type III in treating experimental infections due to this type of *Pneumococcus* in monkeys. Reports of the clinical application of the enzyme are anticipated. Thus far no specific therapy has been developed for infection with *Pneumococcus* type III. The outlook for overcoming pneumonia in general is dealt with in a general review by Cole.¹²

8. Blake, F. G.; Howard, M. E., and Hull, W. S.: The Treatment of Lobar Pneumonia by Artificial Pneumothorax, *Tr. A. Am. Physicians* **49**:119, 1934.

9. Behrend, A., and Cowper, R. B. G.: Artificial Pneumothorax in the Treatment of Lobar Pneumonia, *J. A. M. A.* **102**:1907 (June 9) 1934.

10. Hines, L. E., and Bennett, D.: Artificial Pneumothorax in the Treatment of Acute Lobar Pneumonia, *Arch. Int. Med.* **55**:100 (Jan.) 1935.

11. Francis, T.; Terrell, E. E.; Dubos, R., and Avery, O. T.: Experimental Type III *Pneumococcus* Pneumonia in Monkeys, *J. Exper. Med.* **59**:641 (May) 1934.

12. Cole, R.: The Outlook for Overcoming Pneumonia, *Canad. M. A. J.* **30**:237, 1934.

It was at one time believed that the intact body of the pneumococcus was required to evoke specific immune bodies, but in recent years evidence has accumulated to indicate the antigenic effectiveness of various soluble derivatives. The subject is discussed by Felton, Sutliff and Steele.¹³ These investigators were able to induce immunity by injecting a number of fractions derived from the pneumococcus. The immunity evoked by minute amounts of certain substances was comparable in degree to that found in the serum of convalescent patients. Certain of the fractions gave rise to a fairly high degree of heterologous immunity, in contrast with vaccines which evoke homologous immunity chiefly.

Influenza.—Highly important studies on the etiology of influenza have been prompted by the original observations of Shope, who showed that influenza in swine was incited by the combination of a form of influenza bacillus and a filtrable virus. Andrewes and his associates¹⁴ in London succeeded in isolating a filtrable virus in cases of influenza in man which could be propagated in ferrets by nasal instillation. The virus isolated was similar immunologically to the one studied by Shope. Andrewes, Laidlaw and Smith¹⁵ subsequently infected mice with the virus. In mice and ferrets the disease was caused by the virus alone without the presence of concomitant bacteria. Immune serum prepared by hyperimmunizing horses with tissue from infected ferrets specifically protected mice against the virus. With the facts arising from these discoveries, it will be possible to investigate the cause of the next outbreak of pandemic influenza and to determine whether it is identical with that of the so-called interpandemic or seasonal influenza. Should this be the case, the value of these contributions cannot be overestimated.

The observations of Andrewes were confirmed by Francis,¹⁶ who studied material obtained from patients during an epidemic of influenza in Puerto Rico, and by Elkeles.^{16a} Eichhorn and Pyle¹⁷ report the interesting observation that the virus obtained by Andrewes induced

13. Felton, L. D.; Sutliff, W. D., and Steele, B. F.: Antigenic Characteristics in Man of Certain Products of Pneumococcus, *J. Infect. Dis.* **56**:101 (March-April) 1935.

14. Smith, W.; Andrewes, C. H., and Laidlaw, P. P.: A Virus Obtained from Influenza Patients, *Lancet* **2**:66 (July 8) 1933.

15. Andrewes, C. H.; Laidlaw, P. P., and Smith, W.: The Susceptibility of Mice to the Virus of Human and Swine Influenza, *Lancet* **2**:859 (Oct. 20) 1934.

16. Francis, T.: Transmission of Influenza by a Filterable Virus, *Science* **80**:457 (Nov. 16) 1934.

16a. Elkeles, G.: Etiology of Influenza, *Prensa méd. argent.* **22**:857 (May) 1935.

17. Eichhorn, A., and Pyle, N. J.: Observations on the Relationship of the Virus of Human Influenza and Dog Distemper, *J. A. M. A.* **102**:2082 (June 23) 1934.

immunity in ferrets against the virus of canine distemper. Nörr^{17a} comments on the relation between influenza in man and canine distemper. Dochez, Mills and Kneeland¹⁸ succeeded in isolating a filtrable virus from patients apparently suffering from influenza which was similar to the agent which they believed to be the causative agent of the common cold. The virus was cultivated in tissue culture and was capable of producing characteristic symptoms in both man and the chimpanzee after many months of cultivation in vitro. Kairies,¹⁹ on the other hand, questions the rôle played by a filtrable virus and still believes that the influenza bacillus of Pfeiffer in symbiosis with the streptococcus is the cause of influenza. Gundel²⁰ thinks that pandemics of influenza are to be attributed more to changes of resistance in the population than to an increase of virulence of the bacteria or to mixed infection. He believes that most observers still favor the hypothesis that the influenza bacillus is the cause.

Rheumatic Fever.—The cause of rheumatic fever remains undetermined. In spite of much investigation incriminating the streptococcus, the proof of its etiologic relationship to the disease has not been established. Numerous authors have attempted to isolate a filtrable virus, but without success. Swift,²¹ in discussing the subject, suggests that the frequent occurrence of nonhemolytic streptococci in the blood during the disease may be due to increased permeability of abnormal mucous membrane, permitting entrance of these bacteria. In regard to the hemolytic streptococcus, Swift cites the work of Todd, who found antistreptolysins in the blood during acute rheumatic fever, and of other investigators who demonstrated precipitins for nucleoproteins of the hemolytic streptococcus. Other observers, however, found both antistreptolysins and precipitins in other diseases as well. Recent studies by Hadfield²² and Myers²³ and their associates show that the plasma of patients with

17a. Nörr, J.: Are There Connections Between Influenza in Human Subjects and Distemper in Dogs? München. med. Wchnschr. **82**:455 (March 21) 1935.

18. Dochez, A. R.; Mills, K. C., and Kneeland, Y.: Studies of the Etiology of Influenza, Proc. Soc. Exper. Biol. & Med. **30**:1017, 1933.

19. Kairies, A.: Die Empfänglichkeit von Iltissen und Frettchen für Influenzabacillen, Ztschr. f. Hyg. u. Infektionskr. **116**:264 (Aug.) 1934.

20. Gundel, M.: Grippeproblem, Deutsche med. Wchnschr. **60**:1575, 1934.

21. Swift, H. F.: Current Conceptions of the Nature of Rheumatic Fever, Tr. Coll. Physicians Philadelphia **2**:152 (Sept.) 1934.

22. Hadfield, G.; Magee, V., and Perry, C. B.: The Lysis of Fibrin by Streptococci, Lancet **1**:834, 1934.

23. Myers, W. K.; Keefer, C. S., and Holmes, W. F.: The Resistance to Fibrinolytic Activity of the Hemolytic Streptococcus with Special Reference to Patients with Rheumatic Fever and Rheumatoid (Atrophic) Arthritis, J. Clin. Investigation **14**:119 (Jan.) 1935.

rheumatic fever is definitely resistant to fibrinolysis by streptococci (page 408). The resistance is comparable to that found in the plasma in cases of erysipelas and other infections due to the hemolytic streptococcus. Myers suggests that this property of the plasma may be due to the streptococcal infection which often precedes rheumatic fever, without necessarily having a specific etiologic relationship to the latter condition.

In discussing allergic reactions to streptococcal nucleoproteins, especially those of the hemolytic streptococcus, Swift states that children with rheumatic fever show a much higher proportion of positive reactions than a group of normal children of similar age. He further points out that patients who have previously had rheumatic fever and contract streptococcal infection are five or six times as likely to have an attack of rheumatic fever as persons who have not had rheumatism previously who contract similar streptococcal infection. The prevention of such an infection would no doubt prevent relapses of rheumatic fever. Aschoff, on the other hand, in an address before the Medical Society of Freiburg stated that the causative agent is not to be sought in any recognized streptococcus. He does not believe that the origin of the specific nodules is an allergic reaction or that allergy plays a rôle in rheumatic fever. He is not convinced of the experimental production of specific nodules.

In another paper Swift²⁴ discusses the chronicity of rheumatic fever as indicated by the granulomatous nature of the typical lesions, the familial or inherited background, prolonged fever, tachycardia, recurring arthritis, subcutaneous fibroid nodules and progressive valvulitis. He also regards chronic nutritional disturbance as an important factor in the disease. This may be due to a general state of undernutrition; to a deficiency of vitamin A, as suggested by Mellanby, or to a lack of vitamin C, according to Rinehart and his associates,²⁵ although the addition of these vitamins to the normal diet had no effect on the progress of the disease. In a paper read at Atlantic City in May, Schultz, Sendroy and Swift reported that lack of vitamins is not important in causing rheumatic fever.

The relationship of rheumatic fever to chronic rheumatoid arthritis is still a moot point. Some investigators have claimed that the transition occasionally seen from rheumatic fever to chronic arthritis in patients indicates a relationship. It seems hazardous, however, to assume an identity of etiologic factors on this basis or on that of the histologic

24. Swift, H. F.: The Chronicity of Rheumatic Fever, *New England J. Med.* **211**:197 (Aug. 2) 1934.

25. Rinehart, J. F.; Connor, C. L., and Mettier, S. R.: Further Observations on the Pathologic Similarities Between Experimental Scurvy Combined with Infection and Rheumatic Fever, *J. Exper. Med.* **59**:97 (Jan.) 1934.

similarity of the subcutaneous nodules observed in each disease; there seems to be no reason why the two diseases cannot attack the same person.

The studies of Von Glahn and Pappenheimer²⁶ do not substantiate the current idea that subacute bacterial endocarditis is the result of infection of old healed or scarred valves after rheumatic fever. Infection of the cardiac valves by nonhemolytic streptococci is due to implantation of bacteria on active or unhealed rheumatic vegetations. The authors express the belief that the continued activity of rheumatic fever is indicated by the invariable occurrence on the valves of the rheumatic verrucae which are free from bacteria, and by the presence of Aschoff bodies in the myocardium in the same percentage of cases in uncomplicated rheumatic carditis.

Chronic Infectious Arthritis.—This important disease has been the subject of extensive investigation during the past few years. At the Third Conference on Rheumatic Diseases²⁷ in June 1934, Steindler presented evidence that foci of infection are present in the same percentage of patients with rheumatoid (infectious) arthritis as of those with degenerative osteo-arthritis. In a high percentage of cases of each type (35 and 20 per cent, respectively) at least temporary improvement was obtained by the removal of foci of infection. Although it would seem that in scattered cases one might be convinced of the relationship of cause and effect between a definite focus of infection and subsequent arthritis, many observers, including the reviewer, are skeptical of the significance attached to the problem and believe it to be greatly exaggerated. A possibility seldom considered in this regard is that persons suffering from arthritis are often in a subnormal state, and as a result the so-called foci of infection may develop.

There seems to be agreement among most observers that two distinct forms exist—rheumatoid (atrophic) arthritis of infectious origin and hypertrophic osteo-arthritis of degenerative origin. It appears also that numerous borderline cases, or those of mixed type, exist which have led some observers to believe that both diseases may be due to the same cause (Archer²⁸ and others).

The controversy regarding positive or negative blood cultures in cases of chronic arthritis is still unsettled. The striking discrepancy between the reports of the investigators who recovered *Streptococcus* from the blood of about 50 per cent of the patients and the recent

26. Von Glahn, W. C., and Pappenheimer, A. M.: Relationship Between Rheumatic and Subacute Bacterial Endocarditis, *Arch. Int. Med.* **55**:173 (Feb.) 1935.

27. Third Conference on Rheumatic Diseases, *J. A. M. A.* **103**:1732 (Dec. 1) 1934.

28. Archer, B. H.: Chronic Nonspecific Arthritis: Etiology and Treatment with Special Reference to Vaccine Therapy, *J. A. M. A.* **102**:1449 (May 5) 1934.

reports of those ²⁹ who seldom find organisms in the blood is an enigma. Myers, Keefer and Holmes ²⁸ have shown that rheumatoid arthritis is not accompanied by an increase in the antifibrinolytic property of the plasma. This observation suggests that the disease process is not associated with or preceded by an active infection with the hemolytic streptococcus.

The use of streptococcus vaccine cannot be considered a specific treatment for rheumatoid arthritis, of course, as long as the cause of the disease is uncertain. Incidentally, there is as yet no proof of a specific beneficial effect of vaccine therapy for any infectious disease. In most of the recent reports the authors ³⁰ minimize the value of vaccine therapy, and many investigators believe that the benefits often obtained are due to nonspecific effects of foreign protein or to other causes. Clinicians of wide experience, such as Kerr and Minot and others, ³¹ have emphasized the importance of regarding arthritis as a systemic disease to be treated by rest, physical and orthopedic therapy, the elimination of foci of infection, change of climate and regulation of the diet ³² as may be required in the individual case. According to Hall and Myers, ³³ there is no direct relationship between dietary factors and the development of chronic arthritis. Excessive consumption of carbohydrates or an apparent vitamin and mineral deficiency has no effect on the incidence of the disease. The subject of chronic arthritis is admirably summarized in a pamphlet prepared by the American Committee for the Control of Rheumatism ³⁴ and by Hench and his associates. ^{34a}

29. (a) Wainwright, C. W.: The Treatment of Chronic Rheumatoid Arthritis with Streptococcus Vaccine, *J. A. M. A.* **103**:1357 (Nov. 3) 1934. (b) Dawson, M. H., and Boots, R. H.: Recent Studies in Rheumatoid (Chronic Infectious, Atropic) Arthritis, *New England J. Med.* **208**:1030 (May 18) 1933. (c) Archer. ²⁸ (d) Cecil. ²⁷

30. (a) Cecil, R. L.: Medical Treatment of Chronic Arthritis, *J. A. M. A.* **103**:1583 (Nov. 24) 1934. (b) Short, C. L.; Dienes, L., and Bauer, W.: Autogenous Vaccines in Rheumatoid Arthritis: A Clinical Study and Critique, *Am. J. M. Sc.* **187**:615 (May) 1934. (c) Cox, K. E., and Hill, D. F.: Chronic Arthritis, *Arch. Int. Med.* **54**:27 (July) 1934. (d) Dawson and Boots. ^{29b}

31. Irons, E. E.: The Treatment of Chronic Arthritis: General Principles, *J. A. M. A.* **103**:1579 (Nov. 24) 1934. Cecil. ^{30a}

32. Bauer, W.: What Should a Patient with Arthritis Eat? *J. A. M. A.* **104**:1 (Jan. 5) 1935.

33. Hall, F. C., and Myers, W. K.: Diet in Chronic Arthritis, *Arch. Int. Med.* **55**:403 (March) 1935.

34. Primer on Rheumatism. Chronic Arthritis, prepared by the American Committee for the Control of Rheumatism and the Committee on Scientific Exhibit, American Medical Association, Chicago, American Medical Association, 1934.

34a. Hench, P. S.; Bauer, W.; Fletcher, A. A.; Ghrist, D.; Hall, F., and White, P.: The Present Status of the Problem of "Rheumatism" and Arthritis, *Ann. Int. Med.* **8**:1315, 1495 and 1673 (April, May and June) 1935.

Tuberculosis.—In a preliminary report of important observations on tuberculosis of the lungs in patients dying from other causes, Terplan ^{34b} points out the impracticability of adhering to a rigid classification of the types of tuberculosis into those occurring in children and those in adults on the basis solely of observations in experiments on animals. The development of progressive tuberculosis is not, except possibly in infancy and early childhood, predominantly determined by the age of the patient. Terplan's studies show that "postprimary" infection (reinfection) may produce complex changes identical with those seen in "primary" tuberculosis (first infection). The first tuberculous infection commonly occurs during the first three decades of life. Primary focal lesions may remain entirely restricted in the lung without changes in the regional lymph nodes.

Wallgren ³⁵ reports the results of observations on 230 children vaccinated with BCG and subjected to exposure to tuberculosis at home. In only 1 of these children did roentgenographic evidence of tuberculosis develop. The children reacted positively to tuberculin after vaccination, which Wallgren believed to be evidence of satisfactory vaccination. These results are at variance with opinions recently expressed to the effect that sensitivity to tuberculin is a liability rather than an asset. The death rate from tuberculosis among infants in Gothenburg was 3.9 per thousand in 1927, the year in which BCG vaccine was introduced. In 1933 the death rate was 0.3 per thousand. It is stated that about 1,000,000 children have thus far been vaccinated without harmful results. Numerous experimental studies ³⁶ have shown that BCG vaccine never causes progressive lesions.

The monograph of Irvine ³⁷ contains a brief but comprehensive discussion of BCG vaccine and an inclusive bibliography. The author shows that a certain increase of immunity is produced in man by the use of the vaccine. He points out that the incidence of tuberculosis has been decreasing steadily in all civilized countries and that in some places in which inoculation is not practiced it is even lower than in countries where BCG vaccine has been in general use, as was also recently pointed out by Boynton.³⁸ While this may be true, the cost of

34b. Terplan, K.: Anatomic Studies of Primary and Postprimary Pulmonary Tuberculosis in White Children and Adults, *Arch. Path.* **17**:723 (May) 1934.

35. Wallgren, A.: Value of Calmette Vaccination in Prevention of Tuberculosis in Childhood, *J. A. M. A.* **103**:1341 (Nov. 3) 1934.

36. Lurie, M.: The Fate of BCG and Associated Changes in Organs of Rabbits, *J. Exper. Med.* **60**:163, 1934.

37. Irvine, K. N.: *The BCG Vaccine*, New York, Oxford University Press, 1934.

38. Boynton, R. E.: The Declining Death Rate from Tuberculosis, *J. A. M. A.* **104**:1875 (May 25) 1935.

achieving this decrease has been enormous; if an effective and inexpensive vaccine could be perfected to accomplish the same result there would be a great saving in national expenditure. Only further research can determine whether B C G vaccine will meet the requirement.

Many studies concerning Löwenstein's claim as to the high incidence of bacteremia in tuberculosis and the etiologic relationship of the tubercle bacillus to a varied list of diseases have been published. Although workers in Löwenstein's laboratory and his students have reported further studies substantiating these claims, most investigators have been unable to confirm his results. The matter is dealt with thoroughly by Wilson.³⁹ A few of the numerous other recent publications are those of Peterson and Lederman,⁴⁰ Maier,⁴¹ Kalbfleisch,⁴² Prica and Zuk⁴³ and Saenz.⁴⁴ It appears that Löwenstein's medium is an excellent one for the cultivation of tubercle bacillus, and that bacteremia occurs in a small percentage of patients with tuberculosis, as would be expected. However, the incidence of bacteremia is far less than that recorded by Löwenstein, and little or no evidence is at hand to confirm his rather absurd contentions that the tubercle bacillus is the cause of chronic arthritis, rheumatic fever, schizophrenia and so forth.

Numerous studies have not confirmed the reports of Fontes, Calmette, Valtis and others regarding a filtrable stage in the so-called life cycle of the tubercle bacillus.⁴⁵ It seems that the tubercle bacillus may pass through filters of the type used by some investigators and that atypical tuberculosis results from inoculation of the filtrate (Walker^{45b}).

39. Wilson, G. S.: Tuberculous Bacillemia, Medical Research Council, Spec. Rep. Ser. 182, London, His Majesty's Stationery Office, 1933.

40. Peterson, W. F., and Lederman, H.: The Frequency of Tubercle Bacilli Bacteremia with Loewenstein's Method, *Am. Rev. Tuberc.* **30**:103 (July) 1934.

41. Maier, E.: The Cultivation of Tubercle Bacilli from the Blood-Stream by Loewenstein's Method, *Am. Rev. Tuberc.* **30**:704 (Dec.) 1934.

42. Kalbfleisch, H. H., and Kalbfleisch, E.: Unsere Erfahrungen mit dem Tuberkelbazillenzüchtungsverfahren nach E. Löwenstein, *Wien. klin. Wchnschr.* **47**:939 (July 27) 1934.

43. Prica, M., and Zuk, A.: Untersuchungen über die Tuberkelbazillen Kultur nach Löwenstein, *Ztschr. f. Hyg. u. Infektionskr.* **116**:507 (Dec.) 1934.

44. Saenz, A.: Etudes sur la bacillémie tuberculeuse, recherches expérimentales et cliniques, *Ann. Inst. Pasteur* **52**:645 (June) 1934.

45. (a) Lange, L.: Zur Frage der Filtrierbarkeit des Tuberkelbazillus, *Zentralbl. f. Bakt.* **115**:542 (Abt. 1) (Dec. 6) 1934. (b) Walker, E. L., and Sweeney, M. A.: Microscopic Demonstration of Acid-Fast Bacilli in Tuberculous Filtrates and the Production of Tuberculous "Ultravirus" Infection in Guinea-Pigs, *J. Infect. Dis.* **54**:182 (March-April) 1934. (c) Cooper, F. B.: The Filtrability of the Acid-Fast Group, *ibid.* **54**:236 (March-April) 1934. (d) Flu, P. C.: Especially Filtrable Form of Tubercle Bacilli, *Nederl. tijdschr. v. geneesk.* **78**:3007 (June 30) 1934.

A report of successful isolation of the active principle of tuberculin for the purpose of the much desired standardization of the tuberculin test is made by Seibert and other investigators.⁴⁶

The experiments of Steiner⁴⁷ failed to support the hypothesis concerning the etiologic relationship of the avian tubercle bacillus to Hodgkin's disease.

Tetanus.—The treatment of tetanus has received consideration in several papers. It is by no means a settled problem. According to Taylor,⁴⁸ the great reliance placed on tetanus antitoxin as an effective therapeutic agent is derived largely from its brilliant results in prophylaxis. Taylor points out that the undue attention devoted to the use of serum therapeutically is actually harmful, since other important features relating to treatment may be neglected. He agrees with the majority of authors who have recently expressed doubt as to the value of serum given after symptoms have appeared. He places greatest emphasis on the treatment of the local wound and advocates either complete excision or complete exposure, even if the wound is healed, in the search for possible foreign bodies. Next in importance is the control of symptoms, preferably with tribrom-ethanol or sodium amytal, and, finally, the injection of a single dose of antitoxin serum (from 3,000 to 6,000 units, intramuscularly) to neutralize any uncombined toxin which may still be in circulation. The use of tremendous doses of antitoxin seems to be unnecessary. Miller and Rogers,⁴⁹ on the other hand, recommend large doses of as high as 300,000 units, given intravenously or intramuscularly. They discuss the uselessness of intraspinal injections of antitoxin.

English investigators⁵⁰ tested the use of curare or curarine in the treatment of tetanus in man and in animals. Curare seems to lessen the continuous rigidity and to relieve the spasms.

Highly important investigations on the pathogenesis of tetanus were made by Professor Abel and his co-workers.⁵¹ In a critical analysis of

46. Seibert, F. B.; Aronson, J. D.; Reichel, J.; Clark, L. F., and Long, E. R.: Purified Protein Derivative: A Standardized Tuberculin for Uniformity in Diagnosis and Epidemiology, *Am. Rev. Tuberc. (supp.)* **30**:707 (Dec.) 1934.

47. Steiner, P. F.: Hodgkin's Disease, *Arch. Path.* **17**:749 (June) 1934.

48. Taylor, F. W.: Study of the Treatment in Acute Tetanus, *J. A. M. A.* **102**:895 (March 24) 1934.

49. Miller, R. H., and Rogers, H.: Present Status of Tetanus with Special Regard to Treatment, *J. A. M. A.* **104**:186 (Jan. 19) 1935.

50. Cole, L.: Tetanus Treated with Curare, *Lancet* **2**:475 (Sept. 1) 1934. Florey, H. W.; Harding, H. E., and Fildes, P.: Treatment of Tetanus, *ibid.* **2**:1036 (Nov. 10) 1934.

51. Abel, J. J.: On Poisons and Diseases and Some Experiments with the Toxin of the Bacillus Tetani, *Science* **79**:121 (Feb. 9) 1934. Abel, J. J.; Evans, E. A.; Hampil, B., and Lee, F. C.: Researches on Tetanus, *Bull. Johns Hopkins Hosp.* **56**:84 (Feb.) 1935.

the problem he points out that the current theories regarding the transportation of toxin from the source via the nerves or their lymphatics are untenable and are the most revolutionary ever proposed in medicine. He states: "The experiments in support of these theories have been so well designed and so skillfully performed by men of the highest standing, and have appeared to be so valid and irrefutable that the unusual and exceptional mode of transport of a soluble substance has been universally accepted as an entirely satisfactory explanation of the facts of the case."

His experiments are designed to show that the toxin reaches the central nervous system only by way of the blood stream. It is unreasonable, he claims, to believe (*a*) that the toxin is transported via the axis-cylinders or the tissue spaces by "protoplasmic streaming," (*b*) that there is a continuous lymphatic system connecting the peripheral nerves with the central nervous system, and (*c*) that the toxin diffuses directly into the central nervous system. The long period of incubation frequently noted in cases of tetanus is not incompatible with the arterial transportation of the toxin, since symptoms are often delayed long after the injection of numerous other chemical toxins. A certain time elapses before symptoms occur even when tetanus toxin is injected intravenously, or several days after the site of the local lesion has been excised.

These experiments of Abel, which appear so convincing, will naturally have an important bearing on the treatment of this disease. As previously mentioned, there is already skepticism regarding the merits of the intraspinal injection of antitoxin, which these experiments, of course, indicate to be worthless. Opinions as to the uselessness of tremendous therapeutic doses of antitoxin are supported if one assumes that the bacillus lives only a short time in the lesion and produces a certain amount of toxin and no more.

Poliomyelitis.—At a symposium held in December 1934⁵² several new methods of vaccination against poliomyelitis were presented, all of which were based on similar principles. They consist for the most part of the use of the living virus treated with chemicals (formaldehyde, phenol and sodium ricinoleate) to reduce its virulence. One method consists of the immunization of monkeys with very minute doses of the living, unattenuated poliomyelitis virus mixed with the active virus of vaccinia and injected intracutaneously. There appears to be no doubt that immune, virus-neutralizing substances can be evoked in animals and in children by the use of these vaccines. The possibility that the so-called attenuated virus may revert to a virulent form or that minute doses may cause infection in susceptible persons necessitates great caution in the

52. Symposium on Poliomyelitis, Science **81**:130 (Feb. 1) 1935.

practical application of this principle. Before injection of the living virus either in minute doses or in its attenuated form is carried out on a large scale in human subjects, convincing evidence will have to be forthcoming insuring the safety of the procedure. Furthermore, the low morbidity rate of poliomyelitis renders the practicability or desirability of vaccination on a large scale questionable. There is as yet no reliable evidence that the vaccine or serum⁵³ is effective in influencing the disease if injected after symptoms have appeared.

Controversy exists as to whether the virus enters the body through the gastro-intestinal tract⁵⁴ or through the upper respiratory tract. Evidence of the demonstration of the virus in human feces is not convincing, but there is considerable evidence to suggest that the virus enters the upper respiratory tract and is spread by droplet infection, according to Brodie and Elvidge.⁵⁵ These investigators demonstrated the neurotropic nature of the virus in experimental poliomyelitis and showed that it travels along the fibers of the olfactory nerve to the central nervous system, where it is propagated along the nerve tracts.

Encephalitis.—Reports of studies on the St. Louis epidemic of encephalitis appear in a symposium published in *The Journal of the American Medical Association*⁵⁶ and in a monograph published by the United States Public Health Service.⁵⁷ Many new questions were raised by this outbreak, and a few have been answered. The disease differed somewhat clinically from the usual form of epidemic encephalitis, but it resembled in many respects, both clinically and pathologically, a type of encephalitis which occurred in Japan in 1924 and that observed in an isolated group of cases in Illinois in 1932. Probably the greatest advance in the knowledge of this disease was the recovery of a filtrable virus which appears to be the cause of the disease. The virus was pathogenic for mice and monkeys and could be propagated in these animals. Webster, Fite and Cox were unable to demonstrate an immunologic relationship between the virus of the disease and that of epidemic encephalitis, poliomyelitis or Japanese encephalitis.

53. Serum Therapy in Poliomyelitis, editorial, J. A. M. A. **103**:262 (July 28) 1934.

54. The Gastro-Intestinal Tract and the Autonomic Nervous System in Poliomyelitis, editorial, J. A. M. A. **103**:840 (Sept. 15) 1934.

55. Brodie, M., and Elvidge, A. R.: The Portal of Entry and Transmission of the Virus of Poliomyelitis, *Science* **79**:235 (March 9) 1934.

56. Symposium on Epidemic Encephalitis, J. A. M. A. **103**:726 (Sept. 8) and 822 (Sept. 15) 1934.

57. Report on the St. Louis Outbreak of Encephalitis, United States Public Health Service, Pub. Health Bull. 214, 1935, p. 1.

Because of experiments reported by Traub,⁵⁸ the conclusions of numerous investigators must be accepted with caution. Traub showed that the intracerebral injection into mice of sterile bouillon provoked symptoms of encephalitis in 60 per cent. The infectious agent was carried by apparently healthy mice and was activated by the injection of the broth. The disease was strikingly like that produced by the intracerebral injection in mice of material obtained from patients with encephalitis. The situation is reminiscent of a similar one a decade ago when McCartney and Olitsky demonstrated in stock rabbits cerebral lesions identical with those believed to have been caused by the inoculation of other rabbits with the virus of human encephalitis. On the other hand, the specific neutralization of the virus believed to be the cause of the St. Louis outbreak by the serum of patients convalescing from encephalitis strongly supports the etiologic relationship of the virus to the disease. Information regarding the mode of spread of the disease is meager, although it appeared to spread from one community to another by contagion. More than one case seldom occurred in a family. Numerous observations seem to point to the mucous membranes of the upper respiratory tract as a portal of entry. Water, milk and mosquitoes apparently played no rôle. The experiments of Webster indicate that specific neutralizing powers appear in the serum of convalescent persons and animals. Mice can be protected actively or passively. Thus far, no effective therapy has been established.

The disease must not be regarded as new. It has probably occurred unrecognized in other localities, as in New York in 1929 and elsewhere. There is every reason to believe that it will appear again. As in many other infectious diseases, such as lobar pneumonia, it is becoming increasingly clear that encephalitis is not an entity due to a single type of virus but that a multiplicity of closely related viruses give rise to diseases which clinically and pathologically may be indistinguishable, but which vary in their specific immunologic characteristics.

Rivers and Scott^{58a} report the occurrence of 2 cases of meningitis caused by a filtrable virus. The virus was immunologically identical with the virus isolated by Traub from mice and with that obtained from a monkey by Armstrong and Lillie. Nevertheless, the authors are confident that their strain was actually derived from the 2 patients they studied.

58. Traub, E.: A Filtrable Virus Recovered from White Mice, *Science* **81**:298 (March 22) 1935.

58a. Rivers, T. M., and Scott, T. F. M.: Meningitis in Man Caused by a Filterable Virus, *Science* **81**:439 (May 3) 1935.

Cancer.—The Oliver-Sharpey lectures of Andrewes,⁵⁹ in which he pointed out indirect and circumstantial evidence in favor of the view that tumors in animals may be of virus origin, require mention in this review. It is suggested that within apparently normal cells of the human body there exists a virus capable of causing cancer. The hypothesis of the parasitic origin of cancer is by no means dead, and many of the recognized facts concerning tumors are consistent with the view that the behavior of tumor cells is essentially due to their infection by a parasitic virus. The tumor of Rous found in fowls, from which a filtrable virus is obtained, resembles a neoplastic growth in several respects: It grows into tissue by infiltration; growth is independent of the needs of the host; metastasis occurs only through the agency of cells, and apart from metastases the disease remains strictly localized. Furthermore, inclusion bodies, which are usually regarded as evidence of the presence and growth of a virus, are occasionally observed in cancerous tissue. In this case it is, however, still uncertain whether or not virus and cancer are present together. Andrewes also presented and discussed a list of virus diseases producing gradations of tissue reactions ranging from necrosis, such as is caused by the virus of foot and mouth disease, to the neoplasia of malignant epithelioma in the series of epithelial reactions, and in the series of connective tissue reactions varying from the necrosis caused by canary pox to the neoplasia of mammalian sarcoma. The gradation from a reaction to virus infection to true neoplasm is made to appear obvious. Certain features of neoplasms, however, are difficult to explain on the hypothesis of a virus origin, and attempts are made to reconcile certain discordant facts.

Andrewes' views are opposed to those of Murphy⁶⁰ and of Lewis,^{60a} who do not favor the theory that spontaneous tumors are due to living organisms. Murphy does not regard the Rous virus as a true virus since (*a*) it can be purified by chemical procedures ordinarily fatal to living things, (*b*) it is not antigenic, and (*c*) it is highly resistant to inactivation by ultraviolet radiation. These objections do not seem important to Andrewes when the facts are closely scrutinized. He also believes that fowl tumors having a filtrable virus and mammalian cancer are not greatly dissimilar. Andrewes' theory on the whole does not postulate that cancer is infectious in the conventional sense, as poliomyelitis, for example. The supposition is that within apparently normal cells there may be a virus capable of causing cancer. Under certain conditions, such

59. Andrewes, C. H.: Viruses in Relation to the Aetiology of Tumours, *Lancet* 2:63 (July 14) and 117 (July 21) 1934.

60. Murphy, J. B.: Experimental Approach to the Cancer Problem, *Bull. Johns Hopkins Hosp.* 56:1 (Jan.) 1935.

60a. Lewis, W. H.: Normal and Malignant Cells, *Science* 81:545 (June 7) 1935.

as continual irritation, the dormant virus is awakened or set free, and a neoplastic growth starts. An analogy is that of the virus of herpes simplex, which appears to reside dormant in many persons until stimulated to growth or permitted to grow by entirely unrelated causes, such as a rise of body temperature, excessive smoking and so on.

Further evidence for the possible relationship of a living virus to malignant disease is presented in a series of papers by Rous and Beard.⁶¹ These investigators studied a disease in rabbits discovered by Shope, known as rabbit papilloma. This disease has the appearance of papilloma, and the lesions are devoid of inclusion bodies. It appears in the skin of wild rabbits and is invasive until it meets obstruction. It is easily transmitted to domestic rabbits, but the causative agent cannot be recovered in active form from these animals. When implanted internally the growths proliferate and frequently cause death. They tend to recur after excision. In a word, the growth possesses the immediate characteristics whereby tumor is recognized. On the other hand, it differs from tumors as a group in its incidence, which is that of an infectious process, and in that its cause has been demonstrated to be a filtrable virus. The authors conclude that the morphologic characteristics and behavior of the generality of tumors can no longer be taken to exclude the possibility that they are produced by extraneous living entities. Murphy⁶² presents arguments to substantiate his views on the matter in another publication.

Ledingham and Gye⁶³ claim to have succeeded in separating the infective agent of avian tumor by centrifugation at high speed. Their description of "experiments 1 and 2," however, is not clear; it reads as though the supernatant fluid were just as effective in producing tumor as the sediment. They found enormous numbers of "elementary bodies" in the deposits and demonstrated agglutinins for these forms in the serum of tumor-bearing fowls. The particles were smaller than those of vaccinia.

Typhus.—Zinsser⁶³ draws attention to the fact that before 1917 typhus fever was regarded as a single entity. At least two varieties of the disease have since been recognized—the classic European and the Mexican or endemic variety (tabardillo). The question arose as to whether the form of typhus fever endemic in the northeastern part of

61. Rous, P., and Beard, J. W.: A Virus-Induced Mammalian Growth with the Characters of a Tumor (the Shope Rabbit Papilloma), *J. Exper. Med.* **60**:701, 723 and 741 (Dec.) 1934.

62. Ledingham, J. C. G., and Gye, W. E.: On the Nature of the Filterable Tumour-Exciting Agent in Avian Sarcomata, *Lancet* **1**:376 (Feb. 16) 1935.

63. Zinsser, H.: Varieties of Typhus Virus and the Epidemiology of the American Form of European Typhus Fever (Brill's Disease), *Am. J. Hyg.* **20**:513 (Nov.) 1934.

the United States (Brill's disease) is a third variety or is identical with one of the two forms just mentioned. Experimentation has shown that Brill's disease behaves in all respects like the European type. It was established that the interepidemic reservoir or source of infection of the endemic (Mexican or murine) variety exists in rats, from which it is transmitted to man by the flea. The interepidemic reservoir of the louse-borne European variety has never been determined. It appeared unlikely that man served this purpose since the virus is demonstrable in the blood of patients for only a short time; furthermore, lice infected with the disease die in a few weeks. With this question in mind, Zinsser studied the problem by investigating the type of person who most frequently contracts Brill's disease. He found that between 1910 and 1933 approximately 90 per cent of all cases occurred among Jews who came from southeastern Europe. About 75 per cent had been in this country for over ten years, so that it was certain that fresh infection from the European source played no rôle. No connection could be traced between the cases, and there was no instance of more than one case in a family. These facts, Zinsser suggests, point to the infected human body as the permanent residence of the virus. It appears that the cases of Brill's disease which have occurred in New York and Boston are recrudescences of typhus fever (perhaps subclinical or latent) resulting from infection acquired at an earlier period in a focus of endemic typhus in Europe. This author has published a highly entertaining and instructive book⁶⁴ on typhus fever.

These views are entirely compatible with a growing mass of evidence concerning latent infection and epidemiology. The dictum "once infected, always infected" seems applicable to certain cases of numerous other infections. It appears to be especially true regarding cases of virus disease, for example, herpes simplex. Evidence of latency and relapses in one form or another is particularly obvious in cases of malaria, tuberculosis, undulant fever and syphilis. These views naturally raise the question of the relation of the healthy carrier to epidemiology in general, and especially of the disposition and treatment of healthy carriers of typhoid and diphtheria bacilli. Is there any hope of freeing these potentially dangerous persons from their infection?

As a result of many recent observations, the interpretation of the etiology of epidemics in general has been altered considerably. The older concepts placed much emphasis on the increase in virulence of comparatively avirulent or dormant organisms to account for illness in persons singly or *en masse*. While the factor of increase of virulence, either as a result of dissociation from an avirulent to a virulent variant or of a presumed change not involving dissociation, appears to be impor-

64. Zinsser, H.: *Rats, Lice and History*, Boston, Little, Brown & Company, 1935.

tant in certain instances, it is apparent that the factors of far greater importance are the change in susceptibility or resistance of the host and the circumstances under which infection is transmitted from the source to the susceptible recipient. This point is especially well illustrated in Zinsser's interpretation: A person who has been infected with the virus of typhus does not become ill, owing to his high resistance. The virus, however, is able to survive in his tissues until some occurrence causes suppression of resistance and permits the dormant virus to proliferate and become invasive. Typhus is not transmitted to other persons in the absence of lice or of some other means permitting the egress of the virus from the patient. Under these circumstances Zinsser predicts that Brill's disease will become extinct spontaneously.

An excellent discussion of the underlying fundamental facts concerning parasitism and disease in general can be found in a recent monograph by Theobald Smith⁶⁵ and, in a more popular form, in Zinsser's recent book.⁶⁴ Otto⁶⁶ reviews the progress made in the study of rickettsial diseases, including tsutsugamushi disease, tropical and Malay typhus, *fièvre boutonneuse*, South African tick fever and São Paulo fever of South America. Some of these diseases appear to be closely related to typhus and others to Rocky Mountain spotted fever.

Evidence of the identity of the murine (Mexican) and the European variety is presented by Mooser, Varela and Pilz.⁶⁷ According to these observers, the epidemic European form can be made to assume the characteristics of the murine variety. They concluded that no real difference exists between the two varieties. The murine (rat) strains represent the original form, whereas the epidemic strains are modifications due to prolonged propagation in the cycle of man-lice-man.

These observations, if they can be confirmed, will be of considerable significance and will furnish one of the first examples of transformation of types. Thus far, for instance, attempts to transform one variety of *Brucella* or of the tubercle bacillus into another have not been successful. On the other hand, the transformation of *Pneumococcus* from one type to another under certain highly artificial circumstances may be regarded as a precedent.

A suggestion is made by Goodman regarding thrombo-angiitis obliterans as a possible late manifestation in cases of typhus fever. Typhus fever is known to be characterized by specific endangiitis. Goodman and

65. Smith, T.: *Parasitism and Disease*, Princeton, N. J., Princeton University Press, 1934.

66. Otto, R.: *Flecktyphus und endemische Fleckfieber*, Deutsche med. Wchnschr. **60**:1299 (Aug. 31) 1934.

67. Mooser, H.; Varela, G., and Pilz, H.: *Experiments on the Conversion of Typhus Strains*, J. Exper. Med. **59**:137 (Feb.) 1934.

Brodie ^{67a} devised a skin test employing a formaldehyde-treated preparation of *Rickettsia* which they claim gave positive reactions in a number of cases of thrombo-angiitis obliterans. It is of interest to add that the latter disease is fairly common in northern China where typhus exists endemically.

Gonorrhea.—A rational discussion of the immunologic aspects of the treatment of gonorrhea of the urogenital tract is presented by Pelouze.⁶⁸ Conservative views of this kind based on critical observation should tend to dampen overenthusiasm in regard to certain modes of immunotherapy. The following points were emphasized: (a) In the presence of disease transient immunity develops lasting from a few months to a year, which appears to be specific and is not protective against the invasion of gonococci of a different type from another source; (b) repeated infections with the same type of gonococcus may eventually induce a symptomless carrier stage; (c) under these circumstances exacerbations may occur under suitable circumstances, and (d) the susceptibility of the host, not the virulence of the gonococcus, determines the severity of the illness. The author believes that the use of gonococcus vaccine may do harm. He thinks that owing to the lack of knowledge of the effect of vaccines used therapeutically their employment is not warranted and that uncritical reports of striking improvement resulting from this or that method of therapy are misleading and retard scientific progress.

In the same issue of *The Journal of the American Medical Association* other papers on the treatment of gonorrhea and an abstract of the discussions are published. The confused state of therapy of this disease is illustrated by the fact that thirteen different remedies, including bacteriophage, chemotherapy and electrical treatment, are championed. The use of gonococcus filtrate is discussed in a paper by Cumming and Burhans.⁶⁹ They believe that the filtrate is of specific value in treating the disease and as a diagnostic agent, but these observations are based on uncontrolled experiments and are unconvincing.

Another enthusiastic report⁷⁰ concerns the use of fever therapy induced by placing the patient in a "fever chamber," on the assumption that the gonococcus is killed by temperature at fever levels. Any report of this nature which claims that "all of the male patients . . . were

67a. Goodman, C., and Brodie, M.: A Test for Diagnosis of Thrombo-Angiitis Obliterans, *Proc. Soc. Exper. Biol. & Med.* **32**:1331 (May) 1935.

68. Pelouze, P. S.: The Immunologic Aspects of Gonococcic Infection, *J. A. M. A.* **103**:1819 (Dec. 15) 1934.

69. Cumming, R. E., and Burhans, R. A.: Experiences with the Gonococcus Filtrate (Corbus-Ferry), *J. A. M. A.* **104**:181 (Jan. 19) 1935.

70. Desjardins, A. U.; Stuhler, L. G., and Popp, W. C.: Fever Therapy for Gonococcus Infections, *J. A. M. A.* **104**:873 (March 16) 1935.

cured" by the method employed must be regarded skeptically. The authors cite several reports of studies in which the gonococcus resisted temperatures as high as 52 C. (125.6 F.) and grew at 40 C. (104 F.), yet they state that "in gonococcus infection there is no doubt that the therapeutic efficacy of fever is absolutely a function of the degree of temperature attained," although the fever produced in their patients averaged 41.7 C. (107 F.). The fact that gonococci could no longer be cultured from the pus does not necessarily indicate their destruction by heat, nor is it certain that recovery when it occurs is due solely to the bactericidal effect of heat.

A more conservative discussion of the beneficial effects of fever therapy on gonorrheal arthritis is given by Hench, Slocumb and Popp.^{70a} Parenthetically, it is not yet proved that elevation of body temperature alone, as caused by diathermy, produces the same effects on the body, other than changes in temperature, as genuine fever induced by infections or the injection of foreign protein. According to several investigators,⁷¹ significant changes in the proteins and lipids of the blood occurred after fever due to infection but not after treatment with diathermy. The value of diathermy in the treatment of infections in general is exaggerated.

Meningococcic Meningitis.—Hoyne⁷² reports good results with the use of a new meningococcus serum containing antitoxin, as developed by Ferry.⁷³ He advocates daily intravenous and intraspinal injections of the antitoxin. It is interesting to note that Hoyne is skeptical of the value of intraspinal therapy and, as in tetanus, believes the intravenous route to be the one of choice. According to his report, the mortality rate in a group of cases was strikingly reduced by the antitoxin as compared with the results obtained with the usual antimeningococcic serum. In 102 patients treated with antitoxin the fatality rate was 20.5 per cent.

Miller⁷⁴ reports a method whereby mice can be infected with meningococcus. The organisms are suspended in mucin and injected

70a. Hench, P. S.; Slocumb, C. H., and Popp, W. C.: Fever Therapy: Results for Gonorrheal Arthritis, Chronic Infectious (Atrophic) Arthritis and Other Forms of "Rheumatism," J. A. M. A. **104**:1779 (May 18) 1935.

71. Moen, J. K.; Medes, G., and Chalek, I.: The Relative Effects of Diathermy and Infection on the Plasma Proteins, Plasma Viscosity and Suspension Stability of the Blood in Dogs, J. Lab. & Clin. Med. **19**:571 (March) 1934. Stoesser, A. V., and McQuarrie, I.: The Influence of Acute Infection and Artificial Fever on the Plasma Lipids, Am. J. Dis. Child. **49**:658 (March) 1935.

72. Hoyne, A. L.: Meningococcic Meningitis: A New Form of Therapy, J. A. M. A. **104**:980 (March 23) 1935.

73. Ferry, N. S., and Steele, A. H.: Active Immunization with Meningococcus Toxin, J. A. M. A. **104**:983 (March 23) 1935.

74. Miller, C. P.: Experimental Meningococcus Infection in Mice, Science **78**:340 (Oct. 13) 1933; Proc. Soc. Exper. Biol. & Med. **32**:1140 (April) 1935.

intraperitoneally. The mice usually die within twenty-four hours. This discovery provides a new method for the study of meningococcic infection. Miller found that antimeningococcus serum was more effective than the new antitoxin in the prevention and treatment of experimental meningococcic infection.

Amebiasis and Amebic Dysentery.—The outbreak of amebic dysentery in Chicago in 1933 aroused widespread interest in the disease. A report of this outbreak is summarized by a number of authorities.⁷⁵ Although no entirely new discovery was made, attention is drawn to several important and often overlooked facts. Amebiasis or infestation with *Endamoeba histolytica* without evidence of illness is far more prevalent than is usually believed. Carriers serve as a perennial source of infection and spread the infection to other persons by contaminating food and drink. Amebic dysentery may be regarded as a manifestation of amebiasis restricted to the large intestine. The specific and the general treatment of the disease have been greatly improved in recent years by the rational use of drugs of the emetine group, organic arsenicals and derivatives of oxyquinoline and other preparations and by dietary management. Successful results from the practical use of new remedies—carbarsone and vioform—in the treatment of amebiasis are reported by Reed and Johnstone.⁷⁶ Many patients treated with these drugs remained free from infection. These investigators discovered that about 10 per cent of 1,000 prisoners were infected with *E. histolytica*.

Experimental studies by Faust and his collaborators are referred to in an editorial in *The Journal of the American Medical Association*.⁷⁷ These investigators found a definite relationship between certain diets and experimental amebiasis in dogs. Raw liver or liver extract and cod liver oil caused rapid improvement in infected dogs. The administration of desiccated stomach or the feeding of canned salmon caused rapid and severe exacerbation of the disease.

75. Craig, C. F.: The Epidemiology of Amebiasis, *J. A. M. A.* **103**:1061 (Oct. 6) 1934. Simon, S. K.: The Clinical Diagnosis of Amebiasis, *ibid.* **103**:1063 (Oct. 6) 1934. McCoy, G. W., and Chesley, A. J.: Control of Amebic Dysentery, *ibid.* **103**:1145 (Oct. 13) 1934. Lynch, K. M.: Prolonged Influences and Complications of Intestinal Amebiasis, *ibid.* **103**:1147 (Oct. 13) 1934. Meleney, H. E.: The Pathology of Amebiasis, *ibid.* **103**:1213 (Oct. 20) 1934. Magath, T. B.: The Laboratory Diagnosis of Amebiasis, *ibid.* **103**:1218 (Oct. 20) 1934. Reed, A. C.: The Treatment of Amebiasis, *ibid.* **103**:1224 (Oct. 20) 1934. Craig, C. F.: Amebiasis and Amebic Dysentery, Springfield, Ill., Charles C. Thomas, Publisher, 1934.

76. Reed, A. C., and Johnstone, H. G.: Amebiasis Among One Thousand Prisoners, *Am. J. Trop. Med.* **14**:181 (March) 1934.

77. Effect of Diet in Experimental Amebiasis, editorial, *J. A. M. A.* **104**:564 (Feb. 16) 1935.

Ulcerative Colitis.—Apropos of the claim that a specific coccus is the cause of ulcerative colitis, Torrey and Montu⁷⁸ present evidence to show that no specificity pertains to various cocci isolated from material obtained from patients with the disease.

As a result of a study of the bacteriologic features of appendicitis, Gundel and his collaborators⁷⁹ believe that appendicitis is an autogenous infection caused by enteric bacteria. The most common form is the enterococcus or the closely related anhemolytic streptococcus. After perforation or in appendical abscess the colon bacillus is the most important organism. In the cases studied there was no relation between the flora of the appendix and that of the throat to suggest that the throat serves as a focus of infection.

Bacillary Dysentery.—Epidemics of dysentery due to the Sonne and the atypical Flexner varieties of dysentery bacilli are reported by Felsen and his co-workers.⁸⁰

Two recent studies⁸¹ have shown that the oral administration of typhoid vaccine gives rise to agglutinins in the blood stream and presumptively provides protection against infection, although to a lesser degree than subcutaneous injections does. The oral method, if subsequently proved reliable, will be of distinct advantage, obviating the unpleasant reactions and after-effects of the vaccine when given subcutaneously.

Mumps.—Johnson and Goodpasture⁸² and Rocchi⁸³ report successful attempts to produce mumps experimentally in animals. Johnson and Goodpasture obtained a filtrable, cytotropic virus from the saliva of 4 of 6 patients with mumps, which when inoculated into monkeys produced acute, nonsuppurative parotitis. The virus has not been found in the saliva of normal persons, and it was free from demonstrable bacteria, including spirochetes.

78. Torrey, J. C., and Montu, E.: The Cultural and Agglutinative Relationships of Intestinal Streptococci, *J. Infect. Dis.* **55**:340 (Nov.-Dec.) 1934.

79. Gundel, M.; Pagel, W., and Süssbrich, F.: Etiology of Appendicitis, *Beitr. z. path. Anat. u. z. allg. Path.* **91**:399, 1933.

80. Felsen, J., and Osofsky, M. A.: Sonne Dysentery, *J. A. M. A.* **103**:966 (Sept. 29) 1934. Felsen, J.; Rundlett, E. V.; Sullivan, J., and Gorenberg, H.: Atypical Flexner Dysentery, *ibid.* **103**:1055 (Oct. 6) 1934.

81. Hakki, A.; Arif, Y., and Ahmet, M.: Parenterale und perorale Immunisierung bei der Typhusprophylaxe, *Arch. f. Schiffs- u. Tropen- Hyg.* **38**:356, 1934. Ruge, H.: Untersuchungen zur Frage der Typhusschutzimpfung, *Zentralbl. f. Bakt. (Abt. 1)* **132**:8, 1934.

82. Johnson, C. D., and Goodpasture, E. W.: An Investigation of the Etiology of Mumps, *J. Exper. Med.* **59**:1 (Jan.) 1934.

83. Rocchi, F.: Etiologia della parotite epidemica: Ricerche sperimentale, *Policlinico (sez. med.)* **41**:223, 1934.

Whooping Cough.—Shibley⁸⁴ published further evidence for ascribing the cause of whooping cough to *Hemophilus pertussis*. During the past few years several attempts have been made to show that the disease is due to a filtrable virus. Shibley succeeded in transmitting a disease resembling whooping cough to an ape by inoculation with influenza bacilli free from virus. The bacilli were later recovered from the trachea and lungs of the animal.

Vaccine prepared from *H. pertussis* has been used by a number of investigators (Sauer and Krueger) with apparent success as a prophylactic agent. These observations further strengthen the view that the disease is caused by *H. pertussis*.

Yellow Fever.—A good review of studies on immunization to yellow fever and a report of original work are published by Findlay.⁸⁵ His observations confirmed the work of Sawyer, Kitchen and Lloyd (1932) in regard to the practical application of immunization to yellow fever by the simultaneous injection of the fixed neurotropic virus of yellow fever and serum of human beings immune to yellow fever. He refers to the possible danger of the method of Sellards and Laigret, who inject virus alone without the addition of immune serum. The severe reactions obtained by this method indicate that slight infection results. In addition, the actual presence of virus in the body serves as a dangerous source of supply for mosquitoes who may happen to imbibe the blood and thereby spread the infection. Findlay reports the results of the vaccination of 200 persons against yellow fever. Immune bodies were present in the serum as long as sixteen months after inoculation. Thus far none of the laboratory workers who were inoculated has contracted the disease. Prior to vaccination accidental infections were common. The development of a practical method of vaccination will render the total eradication of the disease possible. Since man is the only known reservoir of infection and since the infection is transmitted by mosquitoes the life span of which does not exceed two hundred and twenty-five days, it would seem that if immunization is successful for even as short a period as one year the disease should become extinct. The situation in this respect is analogous to that in typhus fever.

Leprosy.—An excellent discussion of the etiology of leprosy has been prepared by McKinley and his colleagues,^{85a} who claim to have

84. Shibley, G. S.: Etiology of Whooping Cough, *Proc. Soc. Exper. Biol. & Med.* **31**:576 (Feb.) 1934.

85. Findlay, G. M.: Immunization Against Yellow Fever, *Tr. Roy. Soc. Trop. Med. & Hyg.* **27**:437 (March) 1934; Recent Contributions to Our Knowledge of Yellow Fever, *Pub. Health Rep.* **50**:360 (March 15) 1935.

85a. McKinley, E. B.: The Etiology of Leprosy, *Medicine* **13**:377 (Dec.) 1934.

isolated and cultivated a micro-organism obtained from lepers which is beyond much doubt *Mycobacterium leprae*. Although all the postulates of Koch have not been fulfilled, the authors succeeded in producing suggestive lesions in monkeys with the isolated organism.

Granulocytopenia.—Although numerous attempts have been made to show that acute agranulocytosis (neutropenia or granulopenia) may be produced experimentally in animals by the use of various bacteria, Meyer and Thewlis⁸⁶ were unable to obtain similar results. Work along these lines has been more striking in clinical experience. Zia and Forkner⁸⁷ report the common association of neutropenia with kala-azar. Agranulocytosis occurred in 4 of 26 cases studied. These observations should answer the question often raised as to whether granulocytopenia is a "new" disease. There is every reason to believe that it is not new but that it has been overlooked, unrecognized or unemphasized, at least in regard to its association with kala-azar. A recent account also appears of a patient in whom acute fatal agranulocytosis developed after two injections of typhoid vaccine. I recently observed a similar phenomenon in a woman who recovered. The patient received two subcutaneous injections of typhoid vaccine a week apart and was admitted to the hospital one day after the last injection with a count of 700 leukocytes and no granulocytes. Miller and Rhoads⁸⁸ succeeded in producing granulopenia in dogs by a special diet. These observations, together with reports of many cases occurring after the administration of various drugs, lead one to suspect strongly that the causes of the syndrome are numerous and nonspecific and that some constitutional factor or sensitivity exists to account for its occasional appearance.

Fusospirochetosis.—There is still much misunderstanding regarding Vincent's disease of the mouth. There is no convincing evidence that the spiral and fusiform organisms so commonly observed in this condition are the etiologic agents. Most critical observers regard them as saprophytes which thrive in necrotic tissue. There is only the merest circumstantial evidence that neoarsphenamine has any influence on the infection. The disease, when untreated, is self-limiting. It has been observed that persons under intensive treatment with neoarsphenamine for other conditions occasionally manifest stomatitis, the lesions of

86. Meyer, O. O., and Thewlis, E. W.: A Report of Failure to Produce Granulopenia with Bacterial Toxins, *J. Clin. Investigation* **13**:437 (May) 1934.

87. Zia, L., and Forkner, C. E.: The Syndrome of Acute Agranulocytosis and Its Occurrence as a Complication of Kala-Azar, *Am. J. M. Sc.* **188**:624 (Nov.) 1934.

88. Miller, D. R., and Rhoads, C. P.: The Experimental Production in Dogs of Acute Stomatitis, Associated with Leucopenia and a Maturation Defect of the Myeloid Element of the Bone Marrow, *J. Exper. Med.* **61**:173 (Feb.) 1935.

which swarm with spiral and fusiform organisms. In spite of this, neoarsphenamine is still officially recommended as the specific therapeutic agent.⁸⁹ Miller and Rhoads⁸⁸ produced ulcerative stomatitis associated with fusiform and spiral organisms, leukopenia and granulopenia in dogs by means of a restricted diet. Lillie⁹⁰ showed lesions in the myelin sheaths of the nerves supplying the oral mucous membranes, and he believes that such lesions are trophic. As a result, suitable conditions for growth are provided for the spirals and fusiform organisms. Lesions could not be produced by direct inoculation of the organisms.

Gas Gangrene.—Reeves⁹¹ calls attention to the common practice of regarding all cases of putrefactive gangrene as instances of a single disease. He shows that about 30 per cent of the cases of this type are due to organisms other than *Clostridium Welchii*. Specific gas bacillus antiserum should not be wasted on the treatment of infections not due to *C. Welchii*. On the other hand, patients suffering from wounds contaminated with soil or street dirt should be given gas gangrene antitoxin prophylactically in addition to treatment by débridement and irrigation.

Unusual and Rare Diseases.—Place and Sutton⁹² present a complete clinical study of erythema arthriticum epidemicum (Haverhill fever), a disease which they, with Willner, described in 1926. It is apparently a newly recognized clinical entity, characterized by an abrupt onset, often with chills, an exanthem and arthritis. The disease occurred as a localized epidemic and was undoubtedly spread by raw milk. The causative organism is believed to be a gram-negative bacillus. It is virulent for white mice and evokes specific agglutinins in rabbits.

Dodd and Tompkins⁹³ report a case of histoplasmosis. The disease was first discovered in Panama in 1906 by Darling, who was in search of a disease analogous to kala-azar on this continent. DeMonbreun⁹⁴ studied the organism recovered from the patient whose case was reported by Dodd and Tompkins and succeeded in reproducing the

89. Fantus, B.: Therapy of Fusospirochetosis (*Fusospirofillosis*), *J. A. M. A.* **104**:741 (March 2) 1935.

90. Lillie, R. D.: Pathology of Experimental Black-Tongue, United States Public Health Service, Nat. Inst. Health Bull. 162 (Sept.) 1933, p. 13.

91. Reeves, J. R.: Infections by Gas-Forming Anaerobic Bacilli, *J. A. M. A.* **104**:326 (Feb. 16) 1935.

92. Place, E. H., and Sutton, L. E.: Erythema Arthriticum Epidemicum (Haverhill Fever), *Arch. Int. Med.* **54**:659 (Nov.) 1934.

93. Dodd, K., and Tompkins, E. H.: A Case of Histoplasmosis of Darling in an Infant, *Am. J. Trop. Med.* **14**:127 (March) 1934.

94. DeMonbreun, W. A.: The Cultivation and Cultural Characteristics of Darling's *Histoplasma Capsulatum*, *Am. J. Trop. Med.* **14**:93 (March) 1934.

REIMANN—INFECTIOUS DISEASES

disease in monkeys. While the causative organism of kala-azar and that of histoplasmosis described by Darling were regarded as a protozoan parasite, DeMonbreun proved the organism in his case to be a fungus. He suggests that the disease be renamed "cytomycosis of Darling." His observations raise the question of whether or not a relationship exists between the organism causing kala-azar and that producing histoplasmosis because of many points of similarity, and invite further study along these lines.

Twenty-four cases of epidemic pleurodynia are reported by Richter and Levine.⁹⁵ This condition appears to be an infectious disease of unknown etiology, characterized by abrupt and excruciating pain in the chest or epigastrium, fever, leukopenia and subsequent recovery. Several cases may occur in a family.

Rivers and Schwentker⁹⁶ succeeded in vaccinating monkeys against psittacosis by intramuscular inoculation with the active virus of psittacosis. Virus introduced intratracheally leads to dangerous illness, whereas virus injected by other routes is harmless and evokes immunity. The intramuscular introduction of the active virus of psittacosis in moderate amounts into human subjects was harmless and led to the development of neutralizing antibodies in the blood. These studies are of importance in respect also to vaccination against poliomyelitis, encephalitis and other infections. It is highly important to determine whether it is true in general that the route of introduction of the virus determines whether illness or subclinical infection and immunity will follow.

Tamura⁹⁷ reports the cultivation of the virus of lymphogranuloma inguinale and its transmission to the guinea-pig.

I⁹⁸ describe a case of infection with *Micrococcus tetragenus*, characterized by purulent arthritis, meningitis and septicemia. A review of the literature revealed that more than 170 cases of this infection have been reported, but almost without exception in the European literature. The infection is probably more common than is generally believed and is either undiagnosed or is mistaken for staphylococcal infection, which it closely resembles.

95. Richter, A. B., and Levine, H. D.: Epidemic Pleurodynia, J. A. M. A. 102:898 (March 24) 1934.

96. Rivers, T. M., and Schwentker, F. F.: Vaccination of Monkeys and Laboratory Workers Against Psittacosis, J. Exper. Med. 60:211, 1934.

97. Tamura, J. T.: Cultivation of the Virus of Lymphogranuloma Inguinale and Its Use in Therapeutic Inoculation: Preliminary Report, J. A. M. A. 103:408 (Aug. 11) 1934.

98. Reimann, H. A.: *Micrococcus Tetragenus* Infection, J. Clin. Investigation 14:311 (May) 1935.

Streptococcus.—Lancefield⁹⁹ shows that hemolytic streptococci can be differentiated serologically by means of the precipitin reaction into the following distinct groups: group A, strains of human origin; those of group B, bovine and dairy origin; group C, those isolated from other animals; group D, those derived from cheese, and group E, those isolated from milk. Later reports indicate the existence of group F, which probably includes the minute streptococci studied by Long and Bliss,¹⁰⁰ and of group G, comprising strains derived from monkeys. Griffith,^{100a} already noted for his fundamental researches on the pneumococcus, has finally succeeded in classifying *Streptococcus pyogenes* (*Streptococcus haemolyticus*), included in Lancefield's group A and associated with scarlet fever, tonsillitis and septic conditions, into distinct types. Many unsuccessful attempts have previously been made, notably the painstaking study of Andrewes¹⁰¹ in 1932. Andrewes confirmed Griffith's earlier work to the extent of noting that three or four forms of the types of streptococci found in scarlet fever have distinctive individuality, but he is pessimistic in regard to the eventual classification of streptococci on the basis of specific agglutination. According to Griffith, there are probably thirty types, twenty-seven of which have been classified according to cultural and serologic specificity. The method of identification is relatively simple and employs the "stained slide" technic of agglutination and the combination of several types of serums into four or five groups. If agglutination occurs in any of the groups the component serums are used separately to identify the type. The analogy to the identification of types of *Pneumococcus* and to the number of different types is indeed striking.

Long and Bliss¹⁰⁰ report studies on the isolation of a new form of minute, amphophilic hemolytic streptococcus. It was isolated from the rhinopharynx in a variety of diseases and from that of normal persons. It will be of interest to determine eventually whether the authors actually isolated a new strain or whether the minute cocci are variant forms of the usual streptococcus.

Fibrinolysis by Streptococci.—Considerable interest has been aroused by the discovery of Tillett, Edwards and Garner¹⁰² in regard to the

99. Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, *J. Exper. Med.* **57**:571 (April) 1933.

100. Long, P. H., and Bliss, E. A.: Studies upon Minute Hemolytic Streptococci, *J. Exper. Med.* **60**:619 (Nov.) 1934.

100a. Griffith, F.: The Serological Classification of *Streptococcus Pyogenes*, *J. Hyg.* **34**:542 (Jan. 5) 1935.

101. Andrewes, F. W., and Christie, E. M.: The Haemolytic Streptococci: Their Grouping by Agglutination, Medical Research Council, Spec. Rep. Ser. 169, p. 1, London, His Majesty's Stationery Office, 1932.

102. Tillett, W. S.; Edwards, L. B., and Garner, R. L.: Fibrinolytic Activity of Hemolytic Streptococci, *J. Clin. Investigation* **13**:47 (Jan.) 1934. Tillett, W. S.: *ibid.* **14**:276 (March) 1935.

REIMANN—INFECTIOUS DISEASES

rapid dissolution of the fibrin clot in human blood by Str. haemolyticus of the beta type obtained from human sources. Fibrinolysis is caused by an enzyme liberated by the organisms.¹⁰² These investigators further demonstrated the development of resistance of the plasma to fibrinolysis in 75 per cent of patients after recovery from infection due to the hemolytic streptococcus. The fibrin clot from the blood of patients who died of this infection was, in no instance capable of inhibiting the fibrinolytic activity. Exacerbations frequently occur in those persons who recover from infection without the development of resistance to fibrinolysis.

These observations are of importance in the understanding of infection due to the hemolytic streptococcus. The reason for the rapid spread of infection in rabbits appeared to be explained readily on the basis of liquefaction of the clot, the presence of antifibrinogenic substances and the inhibition of inflammatory fixation as a result.¹⁰³ However, as Menkin¹⁰⁴ points out, the original investigations showed that the clot in the normal rabbit is resistant to dissolution by streptococci. Menkin believes that the invasive capacity is referable to the mild local effects of the organism as compared with the pronounced locally injurious action of *Staphylococcus aureus*. The clinical application of the fibrinolytic test is referred to in the section on rheumatic fever (page 386).

Microbic Dissociation.—In the light of recent studies, the phenomenon of microbic dissociation appears to be far more complex than the simple change from the S to the R form or from the M to the S to the R form, so intensively studied during the past decade. Baerthelin, in 1918, and other workers reported the existence of a multiplicity of variants of different organisms, and in 1932 Hoffstadt and Youmans reported the isolation of eight variant forms of a single strain of *Staph. aureus*. Dawson¹⁰⁵ demonstrated the existence of at least three variants of the pneumococcus, and Paul¹⁰⁶ notes the occurrence of numerous intermediate forms. Eaton¹⁰⁷ reports an entirely different class of pneumococcus dissociants, which are characterized by autolytic properties at 37 C. (98.6 F.). These so-called P-C variants have been recovered from patients with pneumonia. Numerous variants of the streptococcus

103. Dennis, E. W., and Berberian, D. A.: A Study on the Mechanism of Invasiveness of Streptococci, J. Exper. Med. **66**:581 (Nov.) 1934.

104. Menkin, V.: Further Studies in Mechanism of Invasiveness of Pyogenic Bacteria, Proc. Soc. Exper. Biol. & Med. **32**:162 (Oct.) 1934.

105. Dawson, M. H.: Variation in the Pneumococcus, J. Path. & Bact. **39**:323. 1934.

106. Paul, J. R.: Pneumococcus Variants, J. Bact. **28**:45 (July) 1934.

107. Eaton, M. D.: Studies on Pneumococcus Variation, J. Bact. **24**:271 (March) 1934.

have also been recently studied by Ward and Lyons.^{107a} Raven¹⁰⁸ demonstrated three variant forms of the gonococcus, one form growing as gram-positive diplococci and another as fusiform gram-negative bacilli. Transformation from one form into another was observed. Reports of extreme examples of dissociation, that is, of transformation of cocci into bacilli and vice versa, are questioned by Holman and Carson¹⁰⁹ on the ground of imperfect technic. I⁹⁸ report the dissociation of *Micrococcus tetragenus* into more than seven variant forms, five of which were distinguished by pigment formation—pink, yellow and brown. The striking differences in colony formation provided a unique opportunity for studies of microbic dissociation.

These studies are only a few of many devoted to the subject, which is of great academic interest. The knowledge gained by the studies appears exceedingly complex, yet many preexisting misunderstandings and uncertainties are thereby explained. Attempts have been made to explain the onset of, and recovery from, infectious disease, as well as the occurrence of epidemics, on the basis of microbic dissociation, but as yet the data are inconclusive. The rôle of the phenomenon appears to be only one of many factors in the etiology of, and recovery from, infectious disease.

The subject of the relationship of vitamins and nutrition to infections has been reviewed by Wilder.¹¹⁰ More data have since been collected by Clausen.¹¹¹ The conclusions he reaches should do much to dampen the ardor of enthusiasts who maintain that there is a relation of vitamins to infection. He concludes that experimental studies have not shown an increase of resistance to infection when the diet of the host has been normal, nor is there evidence to support the belief that the administration of vitamins after the onset of acute infection exercises a beneficial effect on resistance. As regards infants, there exists beyond doubt a constitutional state characterized by susceptibility to infection and loss of resistance. Many features besides diet contribute to this state.

In regard to the inheritance of resistance to bacterial infection the reader is referred to an excellent review of experimental studies by

107a. Ward, H. K., and Lyons, C.: Studies on the Hemolytic Streptococci of Human Origin, *J. Exper. Med.* **61**:515 (April) 1935.

108. Raven, C.: Dissociation of the Gonococcus, *J. Infect. Dis.* **55**:328 (Nov.-Dec.) 1934.

109. Holman, W. L., and Carson, A. E.: Technical Errors in Studies of Bacterial Variation, *J. Infect. Dis.* **56**:165 (March-April) 1935.

110. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition, *Arch. Int. Med.* **55**:304 (Feb.) 1935.

111. Clausen, S. W.: Nutrition and Infection, *J. A. M. A.* **104**:793 (March 9) 1935.

REIMANN—INFECTIOUS DISEASES

Hill.¹¹² It has been established that between strains of the same species differences in the mortality rate from specific infections exist which can be ascribed to variations in genetic composition. Various strains of mice differ widely in their reaction to *Bacillus enteritidis*, for example. On the other hand, more than fifty generations of inbreeding did not lead to complete uniformity of the litter in the reaction to infection, but the possibility of breeding a strain with fairly fixed factors of resistance or susceptibility seems reasonable.

Bacteriophage therapy,¹¹³ allergy in regard to immunity¹¹⁴ and recent advances concerning the staphylococcus¹¹⁵ have been thoroughly dealt with elsewhere and need no further comment in this review. Recent advances in syphilis will be discussed in a forthcoming article.

112. Hill, A. B.: *The Inheritance of Resistance to Bacterial Infection in Animal Species*, Medical Research Council, Spec. Rep. Ser. 196, London, His Majesty's Stationery Office, 1934.

113. Eaton, M. D., and Bayne-Jones, S.: *Bacteriophage Therapy*, J. A. M. A. **103**:1769 (Dec. 8); 1847 (Dec. 15), and 1934 (Dec. 22) 1934.

114. Rackemann, F. M.: *Allergy: A Review of Current Literature*, Arch. Int. Med. **55**:141 (Jan.) 1935.

115. Holman, W. L.: *Progress of Medical Science: Studies on Staphylococci*, Am. J. M. Sc. **189**:436 (March) 1935.

Book Reviews

The Brain as an Organ: Its Postmortem Study and Interpretation. By Frederic Wertham, Assistant Professor of Psychiatry, New York University and Bellevue Hospital Medical College; Senior Psychiatrist, Bellevue Hospital; and Florence Wertham. Introduction by Adolf Meyer. Price, \$7.50. Pp. 538, with 166 illustrations. New York: The Macmillan Company, 1934.

This volume deals with the histopathology of the nervous system, mainly the brain, and with clinical correlations, the approach throughout being made from the view that the nervous system should be treated as a functional whole, a totality that is responsive in certain defined ways to the introduction of disturbing influences. In keeping with this position, the authors stress the desirability of making more extensive surveys in histopathologic examinations of the nervous system, recognizing that the distribution of lesions ranks in importance with their kind or quality. Emphasis is placed on the fact that the variety of histopathologic processes is limited, and that the same types of lesions may arise under dissimilar pathogenetic circumstances, thus indicating the need for caution in ascribing particular clinical conditions to specifically characteristic lesions.

The brief first chapter is devoted to orientation, introducing the reader to the objective and point of view of the work. This is followed by two chapters dealing with the technic of the pathologic examination, both gross and histologic, giving a comprehensive and critical outline of procedures. Chapter VII provides a highly important discussion of "The Extent of the Normal." Four chapters are concerned with descriptive accounts of lesions, including their distribution and interpretation. The remainder of the book is made up of clinicopathologic discussions: "Correlation of Lesions with Psychopathological Phenomena"; "Comparative Histopathology"; "Some Histopathological Syndromes That May Be Associated with Mental Disorder"; "Is There a Histopathology of Schizophrenia?" and "Forensic Neurohistology." A selected bibliography contains 117 titles. Grouped together in the back of the volume are 166 excellent plates, mostly drawings reproduced by the aquatone process and photomicrographs. The book is well indexed.

Dietetics for the Clinician. Milton Arlanden Bridges. Second edition. Price, \$10. Pp. 970. Philadelphia: Lea & Febiger, 1935.

The first edition of the book was reviewed for the ARCHIVES in the issue of September 1933. Certain items which were objected to then have received attention. Not noticed before but found in this reviewing are the sample menus for the ketogenic diet. These provide so much carbohydrate that they could not possibly be ketogenic.

The first edition was well received, and this amplified second edition with its extensive and valuable tables will prove to be a useful volume to have on hand for ready reference in dietetic matters.

News and Comment

TENTH INTERNATIONAL CONGRESS OF THE HISTORY OF MEDICINE

The Tenth International Congress of the History of Medicine is to be held in Madrid from September 23 to 29. An especially attractive program is offered during the meetings of the congress, and arrangements have been made by the committee in charge for various tours of especial interest. The official delegates of the United States are Dr. Henry Sigerist of Baltimore, Dr. Howard Dittrick of Cleveland and Dr. Edward B. Krumbhaar of Philadelphia.

TREATMENT OF SEVERE DIABETIC ACIDOSIS

A COMPARISON OF METHODS, WITH PARTICULAR REFERENCE TO THE
USE OF RACEMIC SODIUM LACTATE

ALEXIS F. HARTMANN, M.D.

WITH THE TECHNICAL ASSISTANCE OF MARIE MORTON

ST. LOUIS

The method of treating severe diabetic intoxication which is used at present in the St. Louis Children's Hospital may be recommended for the following reasons: (1) It provides a rapid, yet safe, method of restoring the normal acid-base balance of the blood in its broadest sense; (2) it leads to rapid abolition of ketosis, hyperglycemia and glycosuria, and (3) it can be carried out as a simple routine by a standardized procedure, requiring usually but from thirty to sixty minutes and little or no assistance from the laboratory (with the possible exception of an occasional determination of carbon dioxide content necessary for establishing with certainty the diagnosis of diabetic acidosis).

The essentials of the treatment are the immediate administration of insulin, repeated in six hours, and the immediate parenteral administration of adequate amounts of rapidly available alkali in the form of isotonic racemic sodium lactate and of electrolyte in the form of hypotonic Ringer's solution. Both the principles and details of the method have gradually evolved during the past twelve years, largely as a result of studies made in the wards and in the laboratory, not only on diabetic acidosis but on other types of change in the acid-base balance in the body which have a bearing on the problem of diabetes.

Chiefly for the purpose of presenting the data the eighty-six patients who constituted the total series will be divided into three groups: Group 1 comprises patients treated with insulin, together with dextrose and Ringer's solution, but without alkali; group 2, patients treated similarly, but also with administration of sodium bicarbonate at the beginning of treatment, and group 3, patients similarly treated, except that racemic sodium lactate was substituted for sodium bicarbonate. This division happens also to be somewhat chronologically descriptive of the experience. When insulin became available, late in 1922, the first few patients were treated effi-

Read before the American Pediatric Society, Asheville, N. C., May 5, 1934

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

ciently¹ by a combination of insulin, sodium bicarbonate and dextrose. Then, for about five years my co-workers and I were misled into believing that alkali had no place in the treatment. Later we reverted to its use in the form of sodium bicarbonate, and for the past four years we have used sodium lactate and have gradually developed our present method of treatment.

RESULTS

Of the eighty-six patients treated during the past twelve years,^{1a} the youngest was an infant 8 months of age, and the oldest, a child aged 15 years. Two patients were under 1 year, and three, under 2 years. There were seven deaths, or a mortality rate of 8 per cent. If the mortality rates for the three groups (table 1) are compared, it becomes apparent that they are almost identical. An analysis of the causes of the deaths is, however, enlightening. Of the four deaths in group 1, treated without alkali, one was due to pneumonia, the acidosis being mild and presumably of little importance; the remaining three occurred between twelve and twenty-four hours after institution of treatment, before the acidosis was relieved. In two of these patients the initial carbon dioxide contents of the serum were low (10.6 and 11.6 volumes per cent, respectively). In the third, a value of 28 volumes per cent was found, but in this instance there is some doubt as to the accuracy of the finding, as it was not checked and immediately after the determination had been made a small leak was found in the apparatus used to measure the volumetric content of the gas. The clinical symptoms in this case suggested much more severe acidosis. In all three instances little or no clinical or laboratory evidence of improvement of the acidosis followed institution of treatment, and death resulted from gradual respiratory and cardiac failure; in two instances it occurred about twelve hours, and in the other, about twenty-four hours after institution of treatment. Postmortem examination was permitted in two of these three cases: In one, that of a girl aged 15, whose initial carbon dioxide content was 28 (?) volumes per cent, no pathologic findings were noted other than cloudy swelling and degeneration of the renal tubules, fatty infiltration of the liver and myocardium, some hemorrhagic areas on the epicardium and congestion of the brain with some small surface hemorrhagic areas near the central

1. Hartmann, A. F.: Diabetes Mellitus in Infants and Children, *M. Clin. North America* 9:69 (July) 1925.

1a. Since this paper was submitted for publication, five more cases have been encountered, making a total of ninety-one. These additional cases, in all of which recovery occurred, included those of an infant of 11 months with an initial carbon dioxide content of 9.6 volumes per cent, of an infant of 22 months with a carbon dioxide content of 11.5 volumes per cent and of three older children with initial carbon dioxide contents of 12.2, 21.7 and 26 volumes per cent respectively. All were treated by the sodium lactate method, and rapid recovery (as defined on page 10) occurred. With these additional cases the mortality in the group of patients treated with sodium lactate has been reduced to 5.7 per cent.

TABLE 1.—Results of Treatment in Eighty-Six Cases of Diabetic Acidosis

Degree of Acidosis, Carbon Dioxide Content of Serum, Vol. %	Total Number of Cases	Type of Treatment											
		Insulin + Ringer's Solution and Solution of Dextrose; no Alkali				Sodium Bicarbonate + Insulin, Ringer's Solution and Solution of Dextrose				Sodium Lactate + Insulin and Ringer's Solution			
		Recovery		Number of Deaths		Recovery		Number of Deaths		Recovery		Number of Deaths	
		Rapid	Slow	Unchecked		Rapid	Slow	Unchecked		Rapid	Slow	Unchecked	
Mild..... (35-45)	14	12	8	2	1*	0	2	2	0	0
Moderately severe..... (25-35)	19	12	2	7	3	0	7	7	0	0
Severe..... (15-25)	29	14	2	7	5	0	6	0	0	9	9	0	0
Extreme..... (15 or under)	24	8	2	6	0	4	4	0	1†	12	12	0	2§
Total number of cases	86	46	14	22	10	4	10	0	1	30	30	0	2

* Death due to pneumonia; acidosis relatively unimportant.

† Death in 2 cases apparently due entirely to effects of acidosis, which was unrelieved.

‡ Death due to pneumonia; acidosis relieved before death.

§ Death in 1 case due to pneumonia, and in another, to hyperthermia; acidosis relieved in each instance.

TABLE 2.—Data on Patients with Diabetic Acidosis Before Treatment (Group I) and Results of Chemical Determinations on Blood Serum.*

Case	Sex	Date	Age, Years	Weight, Kg.	Carbon Dioxide Content, Vol. %	pH	Sodium Chloride, Mg. per 100 Cc.	Proteins, per Cent	Inorganic Phosphorus, Mg. per 100 Cc.	Lactic Acid, Mg. per 100 Cc.	Total Base, Millimols	BR,† Millimols	Dextrose, Mg. per 100 Cc.	Non-protein Nitrogen, Mg. per 100 Cc.	Outcome
1	M	2/14/24	6½	14.5	10.6	237	32.0	Died
2	F	8/24/26	12	28.0	15.0	7.10	470	Recovered
3	M	9/16/26	8	20.0	11.0	7.00	497	9.99 (R)	5.6	22.4	119	7.0	488	37.8	Recovered
4	F	1/26/27	14	50.0	13.8	(7.10)	579	9.99 (R)	5.8	(18.0)	147	17.0	457	36.8	Recovered
5	F	2/11/25	12	35.0	18.4	6.97	579	475	30.8	Recovered
6	F	3/31/24	13	37.0	13.4	480	43.6	Recovered
7	F	2/ 1/27	12	25.0	25.0	396	Recovered
8	M	6/ 3/26	10	25.0	14.6	7.17	538	9.99 (R)	(5.6)	(18.0)	128	6.0	516	52.2	Recovered
9	F	4/ 4/27	7	20.0	23.5	7.25	562	8.28 (R)	...	13.9	210	26.0	Recovered
10	M	1/23/24	6	14.0	22.0	318	Recovered
11	M	10/29/23	12½	25.0	19.9	27.9	292	48.2	Recovered
12	F	9/25/25	12	20.0	19.6	579	290	29.0	Recovered
13	M	12/ 5/27	13	40.0	20.3	527	10.41 (R)	...	33.1	479	35.0	Recovered
14	M	5/26/28	15	45.7	25.3	7.10	544	8.23 (K)	(5.6)	15.1	150	27.0	492	36.6	Recovered
15	M	1/17/25	2½	9.9	20.7	538	305	46.6	Recovered
16	F	2/13/25	12	35.0	19.8	332	23.4	Recovered
17	F	1/25/27	14	50.0	12.7	565	9.13 (R)	386	29.6	Recovered
18	F	8/ 4/26	13	40.0	18.0	389	44.0	Recovered

* (R) indicates determination by refractometer, and (K) determination by micro-Kjeldahl procedure. The figures in parentheses are assumed values necessary for calculation of BR.

† The figures in this column indicate the salts of residual acids (R) left after the determination of the specific ones indicated (Cl, HCO₃, protein, phosphate and lactate).

gyrus. The postmortem examination in the other case, that of a 7 year old boy, whose initial carbon dioxide content was 10.6 volumes per cent (case 1, table 2, chart 1), revealed mural thrombi in both ventricles and evidence of fresh bronchopneumonia in addition to tonsillitis, otitis media and stomatitis. There was also fatty degeneration of the heart, kidneys and liver. Glycogen stains of the liver, however, showed that the glycogen content was markedly increased. In the instance in which postmortem examination was not permitted the diabetic acidosis seemed uncomplicated and appeared to be the direct cause of death.

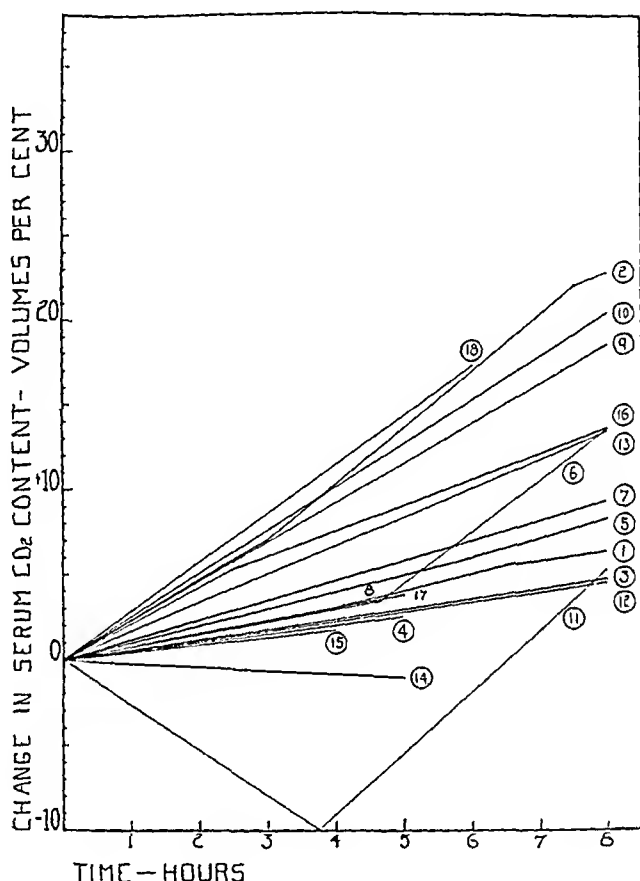


Chart 1.—Curves showing rate of recovery from diabetic acidosis when the treatment consisted of insulin, water, Ringer's solution and dextrose solution, but no alkali. The doses of insulin per kilogram of body weight were as follows: case 1, 5.5 units; case 2, 3.6 units; case 3, 3 units; case 4, 3 units; case 5, 2.9 units; case 6, 2.8 units; case 7, 2.4 units; case 8, 1.8 units; case 9, 1.5 units; case 10, 1.5 units; case 11, 1.1 units; case 12, 1.3 units; case 13, 1.3 units; case 14, 1.1 units; case 15, 1 unit; case 16, 1 unit; case 17, 1 unit, and case 18, 0.9 unit. The average dose was 2 units per kilogram of body weight.

The single death in group 2, treated with sodium bicarbonate (case 1, table 3, chart 2), occurred about seventeen hours after the patient's admission. The carbon dioxide content had increased from 7.8 to 48 volumes per cent, and ketosis had disappeared, but circulatory failure with marked oliguria persisted. The temperature on admission was 104.5 F.; it rose to 106.5 F. before death. A few fine râles were heard

TABLE 4.—Data on Patients with Diabetic Acidosis Before Treatment (Group 3) and Results of Chemical Determinations on Blood Serum

Case	Sex	Date	Age, Years	Weight, Kg.	Carbon Dioxide Content, Vol. %	pH	Sodium Chloride, Mg. per 100 Ce.	Proteins, per Cent	Inorganic Phos- phorus, Mg. per 100 Ce.	Lactic Acid, Mg. per 100 Ce.	Total Base, Millimols	BR, Millimols	Dextrose, Mg. per 100 Ce.	Non- protein Nitrogen, Mg. per 100 Ce.	Outcome
1	F	12/20/30	11	35.0	8.5	...	600	10.5 (K)	5.7	537	47.0	Died
2	F	7/14/31	6	15.5±	10.8	560	Died
3	M	5/30/33	21	44.0	14.4	...	562	10.7 (K)	588	49.0	Recovered
4	F	6/12/33	11 mos.	7.3	15.0	300	Recovered
5	F	2/23/33	8 mos.	6.4	12.8	...	696	9.02 (K)	4.7	32.2	628	50.0	Recovered
6	F	10/ 6/33	2½	11.3	10.4	...	596	8.72 (K)	...	32.8	525	37.5	Recovered
7	F	7/ 7/30	3	9.6	20.3	...	521	26.4	508	Recovered
8	M	5/12/32	10	27.0	11.4	...	595	6.70 (K)	360	32.0	Recovered
9	F	4/ 4/32	13	45.0	17.0	...	573	8.85 (K)	4.5	52.1	420	30.0	Recovered
10	M	12/20/32	6	17.7	15.1	...	579	8.99 (K)	...	30.2	500	31.0	Recovered
11	M	5/ 1/31	12	30.0	16.1	(7.1)	603	8.58 (K)	3.9	61.3	143	8.4	508	27.0	Recovered
12	M	1/28/31	10	25.0	14.4	...	503	8.41 (K)	655	53.5	Recovered
13	M	7/26/32	4½	14.5	16.2	...	608	6.96 (K)	...	23.9	437	37.0	Recovered
14	F	2/29/32	9	21.9	13.6	7.0	544	7.00 (K)	4.2	32.0	33.0	Recovered
15	M	8/21/31	12	30.0	15.0	316	Recovered
16	F	12/18/30	12	35.4	24.8	25.2	315	Recovered

* (K) indicates determination by micro-Kjeldahl procedure. The figures in parentheses indicate assumed values necessary for calculation of BR.

hyperpyrexia was not determined with certainty, permission for autopsy being refused, but the condition may have been due in part to the method of administration of the lactate solution and will be discussed later. In the other case (case 2, table 4, chart 3) death occurred about four hours after onset of treatment, the temperature rising from 104 F. to 108 F. The history and physical findings indicated the presence of pneumonia. Autopsy was not permitted. During the brief period of treatment, the carbon dioxide content had risen from 10.8 to 47 volumes per cent.

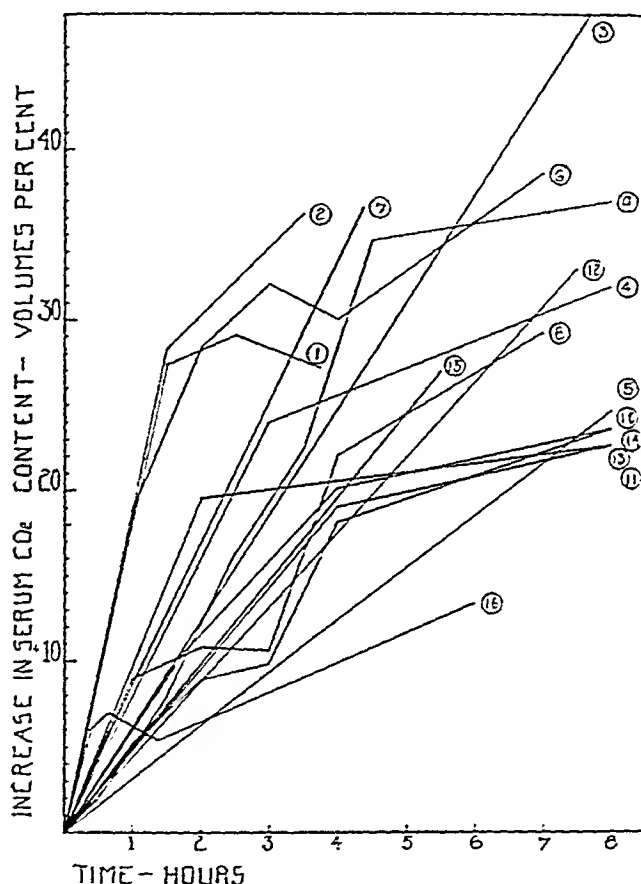


Chart 3.—Curves showing rate of recovery from diabetic acidosis when the treatment consisted of sodium lactate plus insulin, water and Ringer's solution. The doses of molar racemic sodium lactate and insulin per kilogram of body weight were as follows: Case 1, 18.5 cc. of sodium lactate and 2.9 units of insulin; case 2, 13.3 cc. of sodium lactate and 5 units of insulin; case 3, 13.2 cc. of sodium lactate and 2.4 units of insulin; case 4, 13 cc. of sodium lactate and 3.6 units of insulin; case 5, 12.5 cc. of sodium lactate and 2.8 units of insulin; case 6, 12.5 cc. of sodium lactate and 2.6 units of insulin; case 7, 11.5 cc. of sodium lactate and 4.2 units of insulin; case 8, 11.1 cc. of sodium lactate and 2.5 units of insulin; case 9, 10 cc. of sodium lactate and 2.5 units of insulin; case 10, 9.6 cc. of sodium lactate and 2.8 units of insulin; case 11, 8.3 cc. of sodium lactate and 3 units of insulin; case 12, 8 cc. of sodium lactate and 2.4 units of insulin; case 13, 6.9 cc. of sodium lactate and 2.5 units of insulin; case 14, 6.8 cc. of sodium lactate and 3.9 units of insulin; case 15, 6.4 cc. of sodium lactate and 1.2 units of insulin; case 16, 3.8 cc. of sodium lactate and 2.9 units of insulin. The average doses per kilogram of body weight were 10.3 cc. for sodium lactate and 3 units for insulin.

When the seven deaths are considered in retrospect it appears that perhaps two patients treated without alkali might have been saved by the present method of treatment, which materially hastens recovery from acidosis. This effect is apparent from an inspection of table 1. By "rapid recovery" is meant a return to normal of the carbon dioxide contents in the zones of mild or moderately severe acidosis within twelve hours and a return to normal, or at least a return into the zone of mild acidosis, of the carbon dioxide contents initially below 25 volumes per

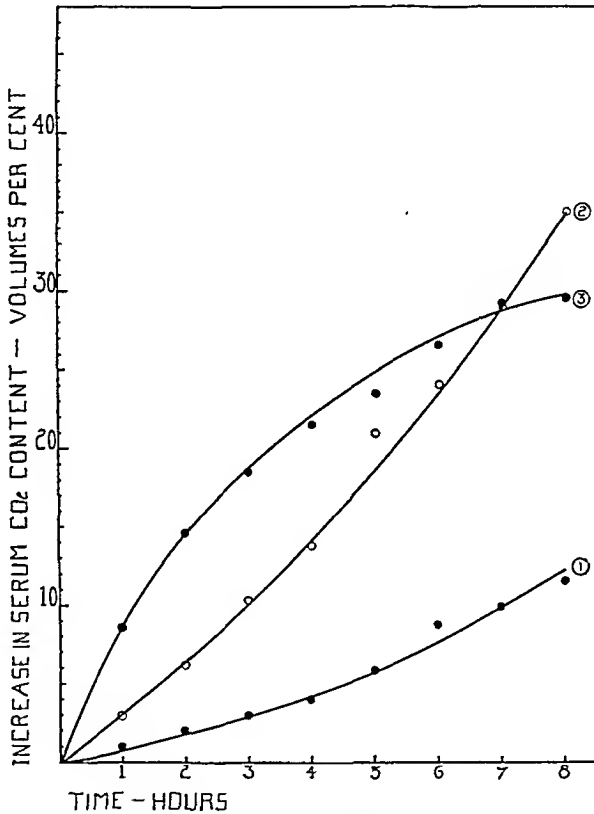


Chart 4.—Curves showing the average response to treatment for groups 1, 2 and 3. The responses in the individual patients constituting these groups are shown in charts 1, 2 and 3, respectively. Group 1 comprised eighteen patients who received an average dose of insulin of 2 units per kilogram of body weight. Group 2 comprises 8 patients treated with molar solution of sodium bicarbonate and insulin. The average dose of sodium bicarbonate was 5.8 cc. per kilogram of body weight; that of insulin, 3.7 units. Group 3 comprises 16 patients treated with molar solution of racemic sodium lactate and insulin. The average dose of sodium lactate was 10.3 cc. per kilogram of body weight; that of insulin, 3 units.

cent. Judged by this standard, in the group of patients not treated with alkali (group 1) a large percentage showed slow recovery. In a number of instances the degree of acidosis actually increased temporarily after institution of treatment.

In order to analyze the effects of treatment more critically, and to compare as fairly as possible the three methods of treatment, it appeared desirable to select from each group all the cases in which the acidosis was of great importance (cases of severe and extreme acidosis) and in which satisfactory follow-up data were secured. Such data are shown in charts 1, 2, 3 and 4 and in tables 2, 3 and 4, and include the results of observations on patients treated up to 1934.

TREATMENT OF PATIENTS WITH SEVERE AND EXTREME DIABETIC ACIDOSIS

Patients Treated Without Sodium Bicarbonate or Sodium Lactate (Group 1).—It may be noted from chart 1 that the speed of recovery as indicated by an increase in the carbon dioxide content of the serum varied considerably in the eighteen patients treated without alkali of any sort. In two instances (cases 11 and 14) an actual increase in severity of the acidosis occurred for a period after the beginning of treatment. The total amount of insulin given to the patients in this group during the first six hours varied from 0.9 to 5.5 units per kilogram of body weight, the average amount being 2 units. That the speed of recovery is not proportional to the size of the dose of insulin is apparent from an inspection of chart 1. The cases are numbered from 1 to 18, in accordance with the amount of insulin administered, the largest dose being administered in case 1 and the smallest, in case 18. As it happened, the patient in case 18 recovered more rapidly, and the patients in cases 1, 3 and 4 showed relatively slow rates of recovery. On the other hand the speed of recovery seemed to some extent related to the original level of the carbon dioxide content and to the duration of acidotic symptoms; in general, the more reduced the level was, and the longer acidosis had existed, the slower was the speed of recovery (table 2). When the average rate of recovery is computed (chart 4), it is found that in this group of eighteen patients the rate of recovery is such that the serum carbon dioxide content increases about 1 volume per cent in each hour for the first four hours and that the rate of increase is then gradually accelerated, so that after eight hours the carbon dioxide content is 11 volumes per cent higher than it was at the beginning of treatment. During this eight hour period little clinical improvement, as a rule, was noted in this group, with the exception of improvement in skin turgor, and sometimes in circulation, the results of the administration of fluids.

Patients Treated with Sodium Bicarbonate (Group 2).—In this group of eight patients (table 3, chart 2) the dose of insulin during the first six hours varied from 6.3 to 1.8 units per kilogram, the average dose being 3.5 units, and the dose of sodium bicarbonate given intra-

venously at the beginning of treatment varied from 12 cc. of a molar solution per kilogram to 3 cc., the average dose being 5.8 cc. The cases are numbered in accordance with the size of the dose of sodium bicarbonate, the patient in case 1 receiving the largest dose and the patient in case 18, the smallest. It can be seen from charts 2 and 4 that recovery in this group was much more rapid than in the group treated without alkali. What was still more striking than the effect on the carbon dioxide content of the serum was the effect noted clinically, the patients in this group showing a much more rapid rate of recovery from hyperpnea and tachycardia. It is also apparent from a study of chart 2 that the speed of recovery during the first two hours is more directly proportional to the dose of bicarbonate than to the dose of insulin. The exception (case 1) is worthy of special comment. The protocol of this case and detailed data incident to the patient's recovery have been published previously.² After administration of insulin, dextrose, Ringer's solution and solution of sodium bicarbonate, the patient remained in a state of shock; the pulse was poor and marked cyanosis persisted. Despite the administration of sodium bicarbonate little immediate increase in the carbon dioxide content of the plasma resulted; instead, great increase in both lactic acid and diacetic acid occurred. Consequently, when improvement of the circulation took place, alkalosis resulted after complete abolition of ketosis. No completely satisfactory explanation of the unusual response has been found at the present time. No clinical symptoms accompanied the development of alkalosis, and recovery was otherwise uneventful. From chart 4 it may be seen that the average result of treatment with sodium bicarbonate is to increase the carbon dioxide content slightly more than 3 volumes per cent per hour for the first four hours. After eight hours the average increase is 35 volumes per cent.

Patients Treated with Sodium Lactate (Group 3).—In this group of 16 cases the dose of sodium lactate given initially varied from 3.8 to 18.5 cc. of a molar solution per kilogram, the average dose being 10.3 cc. As in the previous groups, the cases are numbered in accordance with the size of the dose of sodium lactate, the patient in case 1 receiving the largest dose. The amount of insulin given during the first six hours varied from 1.2 to 5 units per kilogram, the average amount being 3 units. From charts 3 and 4 it may be seen that for the group as a whole recovery was more rapid than in either of the other two groups. Again

2. Hartmann, A. F., and Darrow, D. C.: Chemical Changes Occurring in the Body as the Result of Certain Diseases: III. The Composition of the Plasma in Severe Diabetic Acidosis and the Changes Taking Place During Recovery, J. Clin. Investigation 6:257 (Oct.) 1928, case 1.

there is a more direct relationship between the speed of recovery during the first one or two hours and the size of the dose of sodium lactate. The most notable exception is case 5, and it proved to be an exception for the following reasons: The patient, the youngest in the series, was 8 months of age and was admitted late in the afternoon with the symptoms of severe acidosis associated with pharyngitis, otitis media and pneumonia. The previous history did not suggest the presence of diabetes, and after a sample of blood was obtained for chemical analysis the routine treatment for severe nondiabetic acidosis was ordered. To this end

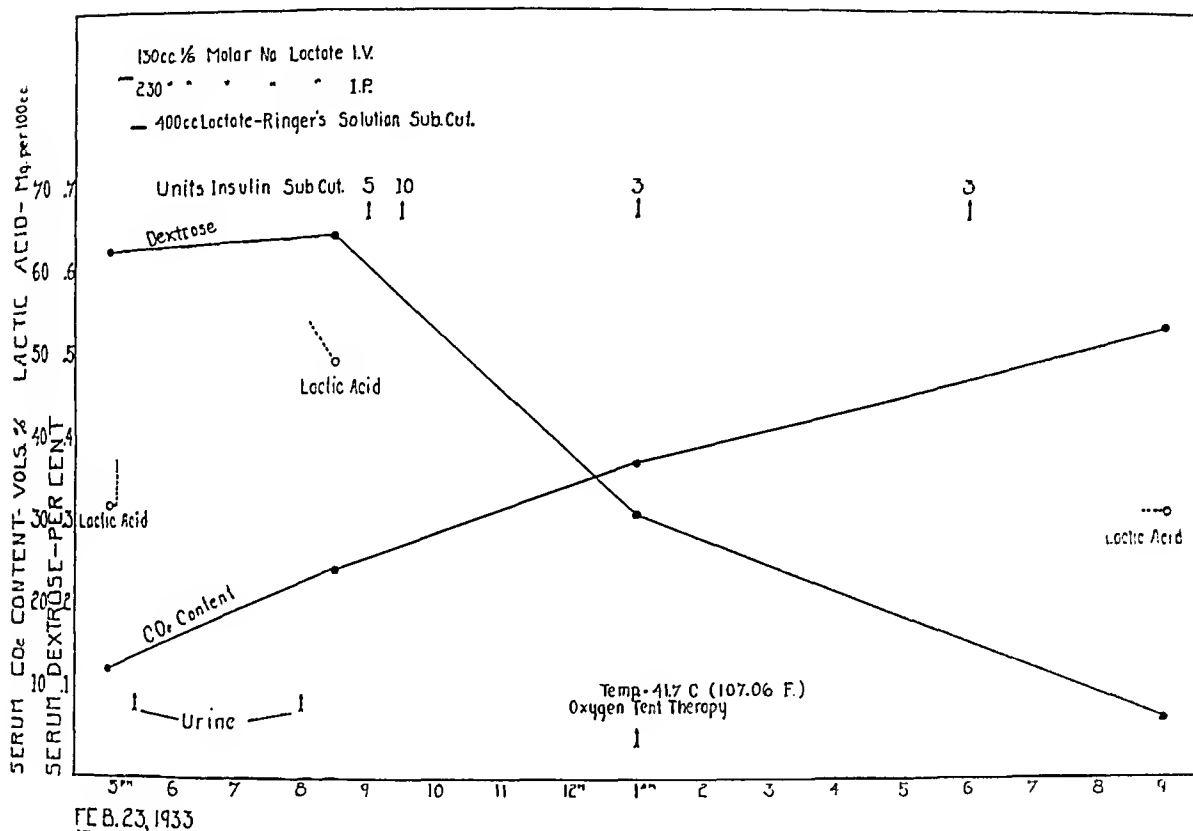


Chart 5.—Curve showing the results of treatment in a case of severe acidosis not immediately recognized as diabetic. The patient was aged 8 months and weighed 6.6 Kg. The immediate treatment consisted of racemic sodium lactate plus lactate-Ringer's solution. Insulin was given later. Pneumonia and otitis media complicated the acidosis.

60 cc. of sixth-molar sodium lactate per kilogram of body weight was given parenterally. During the next four hours the patient showed improvement clinically, and the carbon dioxide content rose from 12.8 to 24.5 volumes per cent (chart 5). At this time, the urine was found to contain sugar, as well as diacetic acid, and the sugar content of the blood was found to be 645 mg. per hundred cubic centimeters. The filtrate made from the initial specimen of blood, which had been set aside in the icebox, was also examined, and the sugar content was found to

be 628 mg. per hundred cubic centimeters. This information made it obvious that diabetic acidosis was present, and insulin was administered in the usual dose of 2 units per kilogram of body weight; after this recovery continued at an accelerated rate. The four hour delay before administration of insulin is, of course, the explanation for the slower recovery in this case. Subsequently this child recovered from pneumonia; later a mastoidectomy had to be performed because of the otitis media. At the time of writing the patient is a healthy-looking infant. This case, of course, demonstrates that metabolism of sodium lactate with formation of sodium bicarbonate takes place in the diabetic state in the absence of insulin administration, a fact which has been previously noted and commented on.³

The average result in these sixteen cases (chart 4) is such as to indicate that almost as much is accomplished during the first hour of treatment with sodium lactate as is accomplished in eight hours when no alkali of any sort is given. The slope of the curve for increase in alkali reserve also differs, being steepest early during the course of treatment, and gradually tapering off as a normal carbon dioxide content is reached. The average gain in carbon dioxide content during the first eight hours was 30 volumes per cent. As in the group treated with sodium bicarbonate, the clinical appearance of improvement tended to coincide with the rise in carbon dioxide content, particularly in regard to dyspnea and tachycardia and to turgor and color of the skin.

Despite the fact that abnormally high initial levels of lactate were present in the blood in a number of cases, in all instances in which it was determined, the concentration of blood lactate had returned to a normal level in from two to four hours after injection of the sodium lactate. In five instances (cases 10, 13 and 14, table 4, chart 3, and two cases observed in 1934) the excretion of lactic acid in the urine was calculated, and it was found that the losses varied from 6.6 to 11.5 per cent of the total amount injected and that the average amount lost through urinary excretion was 8.3 per cent.

In addition to its effect of increasing the alkali reserve, the large amounts of isotonic solution of sodium lactate do, of course, tend to relieve dehydration (as indicated by skin turgor and body weight) and anhydremia (as indicated by a fall in the protein concentration and a rise in the water content of the serum). The administration of Ringer's solution (or lactate-Ringer's solution) in an amount equivalent to 40 cc. per kilogram of body weight immediately after the administration of sodium lactate aids further in relieving dehydration and

3. Hartmann, A. F., and Darrow, D. C.: *J. Clin. Investigation* 6:257 (Oct.) 1928.

at the same time restores lost electrolytes (sodium, potassium, calcium, magnesium and chloride ions). Consequently, with the complete abolition of ketosis,⁴ which usually occurs between six and eighteen hours after treatment is instituted, recovery of the acid-base balance of the blood in its broadest sense tends to be completed during the first twelve hours of treatment, entirely without dependence on absorption from the gastro-intestinal tract and with but a minimal amount of assistance from renal activity.

The curves for the amount of sugar in the blood in the individual cases and the curve for the average amount of the group are shown in chart 6. In this group of cases, as a rule, 2 units of insulin per kilo-

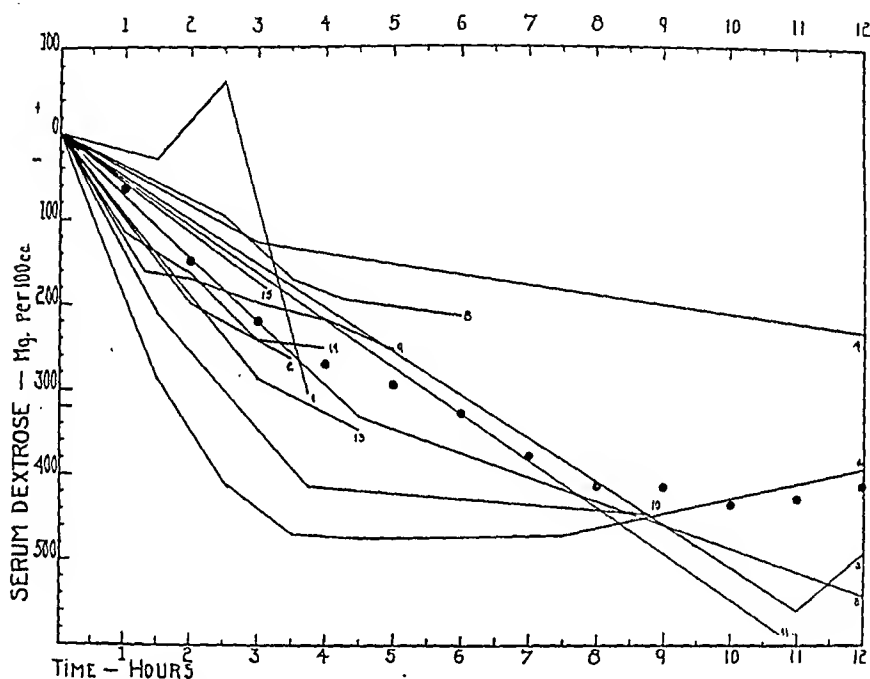


Chart 6.—Curves showing the values for serum dextrose in the group of patients treated with sodium lactate. The average values are shown in large dots.

4. In addition to the testing for diacetic acid in the urine by addition of ferric chloride, a number of other checks on the state of ketosis were usually made. Whenever protein-free filtrates of the serum were prepared for the determination of lactic acid, preliminary distillation of the acidified filtrates was made, the acetone preformed and that resulting from the decomposition of aceto-acetic acid being caught either in Scott-Wilson reagent as a qualitative test for acetone or in alkaline iodine solution for quantitative estimation. When determinations of total base content were made in addition to determinations of the most important normally occurring acids (chloride, bicarbonate, protein, phosphate and lactate), the remaining acid, of course, served as an additional check on the concentration of the ketone acids. In a few instances, when cooperation could be obtained, expired air was blown through the Scott-Wilson reagent to check for the presence of acetone in the alveolar air.

gram of body weight (one half of the dose being administered intravenously and one half subcutaneously) were given at the start, and from four to six hours later another unit per kilogram was given subcutaneously. In two instances (cases 3 and 6) hypoglycemia (without clinical symptoms) occurred between eight and twelve hours after the onset of treatment. For this reason, in the method of treatment used at present the second dose of insulin is reduced to one-half unit per kilogram and is given six hours after the initial dose.

COMMENT

In a recent paper on the pathogenesis and prognosis of diabetic coma, Bertram⁵ in reviewing the literature from 1922 to 1932 included the figures given for mortality rates in twenty-five different series of cases. The figures varied between 5.6 and 73.9 per cent, the average rate for the twenty-five series reviewed being 29.1 per cent. The mortality rate of 8 per cent in the entire series of eighty-six cases described in this article compares favorably with these figures, the results being excelled only in Petrén's series.⁶ As Bertram pointed out, however, such variation in mortality rates is due not only to differences in methods of treatment but also to differences in material, particularly as regards severity of acidosis and of complications. These points should also be borne in mind in considering the extremely low mortality rate among the children and adolescent patients who formed the basis of Joslin's study recently reported by White.⁷ Only one death occurred in seventy cases. In view of such a low mortality rate it is no wonder that Joslin and his co-workers believed that no improvement need be sought for their method of treatment, which excludes alkali with the exception of that derived from fruit juices taken by mouth. It should be remembered, however, that of forty-six of the patients in this series treated in essentially the same manner as that advocated by Joslin and his co-workers four died and that in many of the fatal cases recorded in the literature the patients had been similarly treated. The exceptionally low mortality rate in Joslin's series may have been due to the fact that a relatively smaller percentage of his patients had serious complicating infections and that circulatory and respiratory collapse were not present or imminent at the time the patients were admitted to the hospital. His data certainly indicate that severe acidosis was present in a fairly high percentage of his

5. Bertram, F.: Pathogenese und Prognose des Coma Diabeticum, *Ergebn. d. inn. Med. u. Kinderh.* **43**:258, 1932.

6. Petrén, K.: Ueber die Gründe der diätetischen Behandlung des Diabetes, besonders des Diabetes Gravis, *München. med. Wchnschr.* **74**:1123, 1927.

7. White, P.: *Diabetes in Childhood and Adolescence*, Philadelphia, Lea & Febiger, 1932.

patients.⁸ That a number of his patients, however, recovered slowly and still had marked acidosis on the second and third days of treatment is apparent from his tabulated data. The question naturally is raised whether or not the children in Joslin's series might not have been still better off had they been relieved of their acidosis more speedily, and whether or not some of his adult patients who died might not have been saved by the judicious use of alkali. In this regard it is apparent from some of his comments⁹ that Joslin has less fear of sustained severe acidosis than of the possibility that alkalosis might develop. I cannot but disagree with such a point of view for a number of reasons: 1. There is abundant experimental and clinical evidence to the effect that death may occur directly from the effects of acid intoxication. As early as 1877, von Walters¹⁰ studied the effect of administration of hydrochloric acid to animals and demonstrated that death occurred when approximately enough acid was administered to neutralize all of the alkaline reserve of the body fluids. In the same studies he also proved that alkali has a life-saving value if given promptly enough. Subsequent experimental work confirmed von Walters' results. In clinical experience in the past it has been a common occurrence to see infants succumb rapidly to the effects of acidosis and dehydration resulting from diarrhea and to find no evidence at autopsy to explain such deaths. On the other hand, it is now taken for granted that measures relieving acidosis and dehydration may either prevent or postpone deaths in such cases. That some tolerance to acidosis may be acquired is readily admitted, particularly when the acidosis is slow to develop, as it often is when it is associated with progressive renal lesions. 2. While severe alkalosis is unquestionably dangerous and may also be fatal, the danger of mild or moderate degrees of alkalosis is overrated, and measures for both prevention and relief are simple and effective.¹¹ Joslin's own experience

8. For the group of children reported on by White,⁷ a number of extremely low figures, values from 3 to 5 volumes per cent, for the carbon dioxide-combining power of the plasma are given. Joslin also mentioned the case of one adult patient who walked into the hospital with a carbon dioxide-combining power of 2 volumes per cent! The accuracy of such values, however, has to be questioned when one considers that expired alveolar air with which plasma is equilibrated contains carbon dioxide in amounts of about 3 volumes per cent and that after equilibration with such alveolar air the carbon dioxide tension in the plasma should be increased over what it was; moreover, when increased acidity occurs combination of carbonic acid with base liberated from the protein buffers should result.

9. Joslin, E. P.: *The Treatment of Diabetes Mellitus*, ed. 4, Philadelphia. Lea & Febiger, 1928.

10. von Walters, F.: *Untersuchungen über die Wirkung der Säuren auf den thierischen Organismus*, Arch. f. exper. Path. u. Pharmacol. 7:148 (Aug.) 1877.

11. Hartmann, A. F.: *Acidosis, Alkalosis and Ketosis*, in Brennemann, J.: *Practice of Pediatrics*, Hagerstown, Md., W. F. Prior Company, Inc., 1935, vol. 1, sect. 2, chap. 1.

with the development of alkalosis in diabetic patients hardly justifies his stand, it seems. His fear of alkali seems to be based chiefly on two cases: In one mild alkalosis developed after treatment without alkali and the patient died about ten days later of cerebral hemorrhages; in the other the patient had been treated in another clinic with an unnecessarily large dose of sodium bicarbonate plus insulin. This patient apparently made a rapid and uneventful recovery from severe acidosis, despite the fact that alkalosis developed subsequently. Treatment of the latter patient with hydrochloric acid was instituted because of the fear of symptoms. It seems that this case might even better have been used as an example of the harmlessness of accidental alkalosis following administration of too much alkali.

The essential point, however, concerning the use of alkali is that advantage may be taken of its effect in hastening recovery from acidosis without fear that dangerous degrees of alkalosis might develop if the proper precautions are taken. The chief factors tending toward the production of alkalosis after administration of alkali plus insulin are: (1) excessive doses of alkali, (2) a reduction in the chloride concentration of the body fluids, (3) the development of edema and oliguria resulting from diminished plasma proteins and (4) the presence of actual renal insufficiency, which may curtail the excretion of excess alkali.

Dosage of Alkali.—If sodium bicarbonate itself is given intravenously, the dose should not exceed 0.5 Gm. per kilogram of body weight, which is sufficient, as a rule, to increase the carbon dioxide content of the plasma by about 15 volumes per cent. If much more is given there is danger of development of alkalosis of either or both of two types: (1) a type due to actual excess of alkali, particularly if oxidation of the ketone acids with liberation of base is occurring at a rapid rate in response to insulin, and (2) a type of alkalosis caused by a deficit of carbon dioxide in the presence of a normal, high or slightly low bicarbonate content. The latter condition tends to develop because in the presence of compensatory hyperpnea during the period of acidosis the tension of carbonic acid is reduced and the intravenous administration of sodium bicarbonate in large amounts may increase the ratio of the bicarbonate to the carbonic acid too rapidly, even though the normal amount of bicarbonate is not exceeded. If sodium lactate is given, approximately the equivalent of 1 Gm. of sodium bicarbonate per kilogram may safely be administered. This amounts to about 60 cc. of the sixth-molar solution per kilogram of body weight. The greater safety afforded by medication with sodium lactate is, of course, due to the fact that the sodium lactate has to be metabolized before it is converted into sodium bicarbonate, and such metabolism requires from two to four

hours for completion after the start of administration. It is important, however, to give the racemic sodium lactate in isotonic strength. An increase of from 25 to 50 per cent over the basal rate of oxygen consumption (apparently due to the oxidation of the d-isomer in the racemic mixture) follows the intravenous administration of racemic sodium lactate to normal human subjects¹² when the preparation is given in amounts equivalent to 7 cc. of molar solution per kilogram of body weight. A similar effect probably occurs in the diabetic patient. If the latter is already dehydrated and a hypertonic solution of sodium lactate is given, it is conceivable that such increase in heat production may raise the body temperature to a dangerous level. My co-workers and I believe that this is the explanation for the hyperpyrexia which occurred in one of our fatal cases (case 1, chart 3, table 4). The sodium lactate was given in molar strength to that patient and also to the patient in case 2. Subsequently a sixth-molar (isotonic) solution was used, and no such hyperpyrexia developed.

Rôle of Chloride Concentration.—The tendency on the part of the blood and body fluids to maintain a normal total electrolyte concentration and osmotic pressure, despite variation in the individual anions, is well known. If, after the normal water content has been restored to the blood and body fluids, the chloride level is much reduced (as it tends to be if severe vomiting and dehydration have occurred previously and saline solution has not been administered), base released by oxidation or urinary excretion of organic acid radicals will be retained in the body fluids in combination with the bicarbonate radical. In such situations alkalosis may occur without administration of alkali and, of course, may be intensified as a result of the giving of alkali. If, however, the chloride level is restored to normal by the administration of sodium chloride or Ringer's solution before oxidation of the organic acids is completed, the base released by the oxidation of such acids finds its way into the urine as bicarbonate and the urinary excretion prevents excess of the alkali in the body fluids.

Edema Following Diabetic Acidosis.—The nature of the dietetic management of diabetes before the discovery of insulin was often such that in severe cases a stage of extreme malnutrition was reached. Patients in whom this occurred must frequently have had a reduction of plasma proteins and "nutritional" edema. Two striking examples of edema of this type occurred in this series because of poor control through diet and insulin medication. During periods of severe acidosis, particularly when the acidosis is accompanied by much vomiting and a

12. Hartmann, A. F.: Unpublished data from the Laboratory of the Department of Pediatrics, Washington University School of Medicine and the St. Louis Children's Hospital.

diminished intake of food, the tendency toward still further reduction of plasma proteins and formation of edema may be entirely masked by the dehydrating effect of the vomiting and the acidosis. On cessation of vomiting and relief from acidosis edema would tend to occur in such cases, particularly if an abundance of fluid containing the sodium ion were given. If conditions were such that an excess of bicarbonate in the body fluids tended to be present the tendency toward edema and oliguria would cause alkalosis to persist, despite administration of sodium chloride. Administration of plasma proteins (citrated whole blood or plasma) or some substitute, such as acacia, would remove such a tendency toward edema and permit the kidney to aid in restoring a normal electrolyte balance in the blood.

Renal Insufficiency.—Aside from the oliguria associated with diminished plasma protein, after severe and prolonged acidosis oliguria or anuria tends to occur because of damage to the kidney. The occurrence of such a renal insufficiency is not confined to patients with diabetes; the condition is frequently seen to follow prolonged states of severe acidosis and dehydration in infants and children suffering from severe diarrhea. The question naturally raised is whether or not such renal damage is not a result of the severe and prolonged acidosis and whether the earliest possible relief from acidosis is not always indicated to prevent such an important complication.

In a recent paper, Kydd¹³ commented on the inadequacy of administering merely water and insulin in the treatment of diabetic acidosis and stressed the value of giving sodium chloride. He also recognized the value of sodium bicarbonate in certain cases and expressed the belief that a combination of sodium bicarbonate and sodium chloride should be used. This was the conclusion which a co-worker and I³ reached several years ago, with the difference that we believed that Ringer's solution was superior to sodium chloride and that administration of dextrose solution also had a place. The advantages of sodium lactate over sodium bicarbonate, which have led us to substitute the one for the other, evidently have not sufficiently impressed Kydd, who erroneously stated that "the solution (sodium lactate) also is not immediately available because it must be given intravenously, and, therefore, cannot be made in advance if non-specific reactions are to be avoided." The ease with which it can be prepared, its stability, its compatibility with other solutions and the facility with which it is tolerated by blood and tissues are, of course, some of the reasons that the use of sodium lactate has been substituted for that of sodium bicarbonate.

13. Kydd, D. M.: Salt and Water in the Treatment of Diabetic Acidosis. *J. Clin. Investigation* 12:1169 (Nov.) 1933.

Method of Administering Sodium Lactate.—In regard to the manner in which sodium lactate may be administered, my co-workers and I have made the following observations: (1) When the entire amount is given subcutaneously in isotonic strength, a slight delay of about two hours occurs in the reaching of the peak of increase in the amount of bicarbonate: (2) when a molar solution of racemic sodium lactate is diluted with 5 volumes of Ringer's solution, the resultant solution is apparently sufficiently hypertonic to delay somewhat its absorption from the peritoneal cavity and subcutaneous tissues; (3) when the entire amount of isotonic sodium lactate is given intravenously at a rapid rate, the quickest

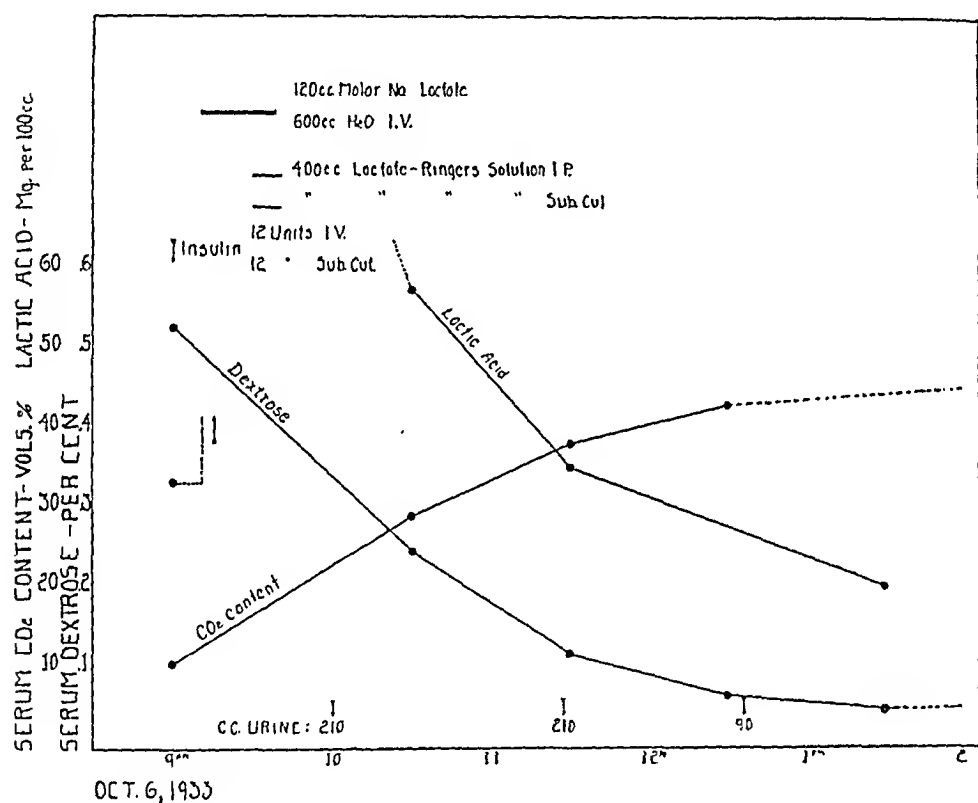


Chart 7.—Curves showing the results of treatment in a patient with severe diabetic acidosis treated by the method which is thought most efficient at the present time, namely, administration of racemic sodium lactate, insulin, and lactate-Ringer's solution. The patient in this case was aged $2\frac{1}{3}$ years and weighed 11.3 Kg.

relief of acidosis results (chart 6); when the sodium lactate is given at a much slower rate by the continuous intravenous drip method, a slower but still satisfactorily rapid recovery from acidosis results. Another method will be tried at the next opportunity which may perhaps prove best of all: The entire amount of the isotonic sodium lactate solution (60 cc. per kilogram of body weight) will be mixed with the entire amount of Ringer's solution (40 cc. per kilogram of body weight) and about one half of the resulting mixture will be given intravenously, the

remainder being administered by a combination of the intraperitoneal and subcutaneous routes.¹⁴

SUMMARY AND CONCLUSIONS

As a result of a critical study on eighty-six patients with diabetic acidosis treated at the St. Louis Children's Hospital during the past twelve years, my co-workers and I have come to the conclusion that the most effective method of treatment demands the use of alkali (sodium bicarbonate or racemic sodium lactate), together with insulin, Ringer's solution and solution of dextrose. When sodium lactate is used instead of sodium bicarbonate, the dextrose solution may be omitted. The method of treatment of severe diabetic acidosis which is recommended at the present time (chart 7) includes:

1. Immediate parenteral administration (one half intravenously, the remainder subcutaneously and intraperitoneally) of 60 cc. of a sixth-molar solution of racemic sodium lactate¹⁵ per kilogram of body weight.

2. Immediate administration of 2 units of insulin per kilogram of body weight.

3. Administration of 40 cc. of Ringer's solution per kilogram of body weight as soon after the administration of sodium lactate as possible.

4. Repeated administration of insulin six hours later in a dose of one-half unit per kilogram of body weight.

5. Transfusion of citrated whole blood or plasma (20 cc. per kilogram of body weight) if edema due to reduced plasma protein develops.

500 South Kingshighway.

14. In two of the five cases encountered since this paper was submitted for publication, this method was used. Apparently a more rapid absorption of the fluid occurred from both the peritoneal cavity and the subcutaneous tissues. A slightly more rapid recovery of the carbon dioxide contents also resulted. Thus, in the last case to be seen, that of an infant of 22 months, weighing 10 Kg., with an initial carbon dioxide content of 11.5 volumes per cent, 600 cc. of one-sixth molar sodium lactate was added to 400 cc. of Ringer's solution; 300 cc. of the mixture was given intravenously and 350 cc. each by the intraperitoneal and subcutaneous routes. Samples of blood were taken at hourly intervals after the administration of fluid was completed. The following carbon dioxide contents were noted: at the first determination, 25; at the second, 34; at the third, 40; at the fourth, 47 volumes per cent, respectively.

15. The racemic sodium lactate used was in sterile 40 cc. ampules of molar strength.

DIFFERENTIAL DIAGNOSIS BETWEEN CEREBRAL HEMORRHAGE AND CEREBRAL THROMBOSIS

A CLINICAL AND PATHOLOGIC STUDY OF 245 CASES

CHARLES D. ARING, M.D.

AND

H. HOUSTON MERRITT, M.D.

BOSTON

The purpose of this study is to present an analysis of 245 cases of lesions of the cerebral vessels in which the diagnosis was proved at necropsy in order to determine the significant findings in the history and examination that will aid in the differential diagnosis between cerebral hemorrhage and cerebral thrombosis.

The average physician rarely attempts to differentiate between these types, and the majority of cases of cerebral vascular lesion are indiscriminately labelled "cerebral hemorrhage." This is true despite the difference in the symptoms, the signs and especially the prognosis of these conditions. Also, with the more recent application of surgical treatment¹ toward the relief of cerebral hemorrhage, it is evident that the treatment becomes even more divergent than that previously advocated. The academic exercise of localizing the lesion, which is so intriguing to the neurologist and internist, must be supplemented by an ability to differentiate the types of lesion. Treatment or the possible alleviation of any cerebral lesion demands accurate knowledge of the nature and location of that lesion. It seems, therefore, that the hope of occasionally relieving the previously almost totally fatal cerebral hemorrhage will force the members of the medical profession to learn not only to localize but to determine more accurately the nature of the process in patients with cerebral vascular lesions. The need of a series of proved cases of cerebral vascular lesions is indisputable and has been repeatedly noted in the literature. Thus, Jones,² after analyzing such a series, concluded "that we stand in great need of a large series of cases of (cerebral) vascular lesions, the history of which has been

From the Department of Neuropathology of the Harvard Medical School and the Neurological Unit of the Boston City Hospital.

1. Bagley, C., Jr.: Spontaneous Cerebral Hemorrhage: Discussion of Four Types with Surgical Considerations, *Arch. Neurol. & Psychiat.* **27**:1133 (May) 1932. Penfield, W.: Surgical Treatment of Spontaneous Cerebral Hemorrhage, *Canad. M. A. J.* **28**:369, 1933.

2. Jones, A. E.: The Onset of Hemiplegia in Vascular Lesions, *Brain* **28**:527, 1905.

critically studied, and the evidences of the lesion before and after death carefully recorded." We have attempted to follow this method in the present study and have selected 245 cases from the records of the Boston City Hospital for the last ten years. Many of the patients admitted to the hospital in the past six years were examined by one or both of us. We found acceptable for this analysis 116 cases of cerebral hemorrhage, 106 cases of cerebral thrombosis and 23 cases of cerebral embolism. The smallness of this series is due to the fact that a number of cases had to be excluded for various reasons, the most important being the lack of an adequate history (despite the fact that a signed necropsy permit was always obtained from the nearest relative) and an incomplete clinical record in which findings probably evident on examination of the patient were not included. These are always the difficulties met with in the use of hospital records for research. Records of many of the cases are not as complete as could be desired, but they suffice for the topic at hand.

The clinical differentiation of cerebral hemorrhage from cerebral thrombosis is not always simple, notwithstanding the present widespread use of the lumbar puncture. The examination of the cerebrospinal fluid is an important factor, but only as an adjunct to a careful evaluation of the history and a thorough physical and neurologic examination. We wish to stress that a carefully taken history and its skilful interpretation are the most important factors not only in the differentiation between cerebral hemorrhage and cerebral thrombosis but also in their differentiation from other cerebral lesions. At times this is a vital matter and may be the only factor at one's disposal for the differentiation of these lesions from (traumatic) subdural hemorrhage. As the latter is relievable in practically 100 per cent of cases in which the diagnosis is made within a reasonable time,³ it is imperative that a thorough history of the patient's illness be obtained as early as possible. In a large general hospital the uniformly poor history of patients presenting evidences of cerebral vascular lesion, especially of those in coma on admission is to be deplored.

ANALYSIS OF THE CLINICAL DATA

We present an analysis of the data obtained from the records of 245 cases of cerebral vascular lesion. We have included 23 cases of cerebral embolism because embolism must be considered in any differential diagnosis of cerebral hemorrhage and cerebral thrombosis, and although the number of cases is not large, they have provided some interesting points.

3. Munro, D.: The Diagnosis and Treatment of Subdural Hematomata, New England J. Med. 22:1145 (May 3) 1934.

Sex Incidence.—Our series indicates that men are more subject to cerebral vascular accidents than women. The preponderance of men was greatest in the group with cerebral thrombosis. The sex distribution in the 116 cases of cerebral hemorrhage was 53 per cent men and 47 per cent women. In the 106 cases of cerebral thrombosis 64 per cent of the patients were men and 36 per cent women, and in the 23 cases of cerebral embolus, 61 per cent of the patients were men and 39 per cent women.

Age Incidence.—As shown in table 1, the majority of the cases of cerebral hemorrhage and cerebral thrombosis occurred in the age group from 50 to 80 years. The average age of the patients with cerebral hemorrhage, 59 years, was somewhat lower than that of the patients with cerebral thrombosis, 64 years. This was due to the fact that a fairly large number of cases of hemorrhage (27) occurred in persons in the years from 30 to 50 years, as compared with 8 cases of cerebral

TABLE 1.—*Age Incidence of Cerebral Vascular Lesions in 245 Cases*

Age, Years	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism	Total
10 to 19.....	1	..	2	3
20 to 29.....	2	2
30 to 39.....	3	1	3	7
40 to 49.....	24	7	3	34
50 to 59.....	31	25	6	62
60 to 69.....	29	37	5	71
70 to 79.....	22	26	..	48
80 to 89.....	2	8	1	11
Not recorded.....	4	2	1	7
	116	106	23	245

thrombosis which occurred in patients in these decades. Also, only 2 of the 11 patients over 80 years of age were in the group with hemorrhage.

The age grouping in the cases of cerebral embolism was not significant. This is explained by the fact that in many cases the embolus arose from the vegetation of the heart valves. The majority of the cases, however, occurred in the age group from 50 to 70 years owing to the frequency of embolism associated with auricular fibrillation in these age groups.

Seasonal Incidence.—The seasonal incidence of onset in our series tends to support Gintrac's ⁴ and Gowers' ⁵ statement that the onset of cerebral vascular injury occurs more frequently in the winter than in the summer. Our cases were distributed as shown in table 2. Approx-

4. Gintrac, E.: *Traité theorique et pratique de l'appareil nerveux*, Paris, Germer-Baillière, 1869, vol. 2, p. 467.

5. Gowers, W. R.: *Diseases of the Nervous System*, ed. 2, London, J. & A. Churchill, 1893, vol. 2, p. 388.

imately 53 per cent of the cases occurred in the five month period from November to March.

Time of Day and Activity.—The time of day of the onset of the cerebral vascular lesion was not significant. In the cases in which this fact was mentioned the onset was found to be fairly evenly distributed among the twenty-four hours. The activity at the time of onset was noted in 53 cases of hemorrhage, 46 cases of thrombosis and 13 cases of embolism. We considered the activity irrelevant (at church, at the theater, bathing, sitting, reading, talking, doing light housework, walking on the street) in 35 cases of hemorrhage, 28 cases of thrombosis and 5 cases of embolism. In 5 cases of cerebral hemorrhage, 9 of cerebral thrombosis and 5 of cerebral embolism the onset occurred while the patient was in the hospital in bed. In 1 case of embolism

TABLE 2.—*Seasonal Incidence of Cerebral Vascular Lesions in 245 Cases*

	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism	Total	Percentage*
January.....	12	14	2	28	12.0
February.....	12	9	3	24	10.3
March.....	13	13	2	28	12.0
April.....	12	6	..	18	7.7
May.....	9	7	1	17	7.3
June.....	12	9	..	21	9.0
July.....	4	5	2	11	4.7
August.....	2	3	2	9	3.8
September.....	7	7	2	16	6.7
October.....	7	11	..	18	7.7
November.....	13	3	6	22	9.4
December.....	13	7	1	21	9.0
Not recorded.....	..	10	2	12	..
	116	106	23	245	

* Percentage of the 221 cases in which the date of onset was noted.

the onset occurred postoperatively, and in another embolism occurred seven days after the administration of digitalis was begun in a patient with auricular fibrillation and congestive heart failure, the pulse falling from 130 to 60 within that period. In 7 cases of hemorrhage, 4 cases of thrombosis and 2 cases of embolism the onset occurred during sleep. In 3 cases of hemorrhage, 1 of thrombosis and 1 of embolism the onset occurred while the patient was eating. We carefully searched for mention of physical or emotional stress as a factor in the onset of cerebral vascular lesion. This was noted in 4 cases of hemorrhage. In 2 the onset occurred while the patient was at work; in the third, during the excitement of watching a wrestling match, and in the fourth, a few minutes after the patient was arrested for peddling merchandise on Sunday. In one case of cerebral thrombosis the condition began while the patient was "straining at stool."

Previous Cerebral Vascular Lesions.—A history of previous cerebral vascular injury was obtained in 14 cases of cerebral hemorrhage; in 58 cases there had been no previous cerebral vascular lesion, and

this point was not recorded in 44 cases. In the cases of cerebral thrombosis, 19 patients had a history of previous cerebral vascular lesion, 47 had none, and in 40 cases this point was not recorded. In the cases of cerebral embolism 6 patients had a history of a previous cerebral vascular lesion; in 13 cases there was no history of such a lesion, and in 4 cases this point was not recorded.

Premonitory Symptoms.—Premonitory symptoms were recorded in 22 cases of cerebral hemorrhage. Sixteen of the patients had headache for periods ranging from two days to (with the severe intermittent type) three years. One of these, who had had a headache of two weeks' duration, complained of localized numbness and slight weakness of the left extremities for one week. In 3 cases there had been mental disturbances for months. In 2 cases there had been attacks of dizziness, in 1 for two and in the other for one year. Drowsiness was recorded in 2 cases, in 1 for a period of one year and in another, in which there was also complaint of headache, for two days. In the cases of cerebral thrombosis, in which the premonitory symptoms are supposed to be fairly common, they were recorded in only 8 instances. This may be due in part to the fact that the records of the cases of cerebral thrombosis were generally poorer than those of the cases of cerebral hemorrhage. Neurologic prodromes were noted in 3 cases. In 1 there had been repeated and numerous attacks of tingling and numbness in the right and the left side of the face and the left extremities for five days before the onset of left hemiplegia. During these attacks the patient's speech was incomprehensible, and the left arm and leg would become rigid and then flaccid, with increased tendon reflexes and an extensor plantar response. Between attacks the patient could use the left arm and leg, and the plantar response was normal. A softening of the right half of the pons was observed at autopsy. Similarly, a second patient noted numbness and tingling of his left upper extremity twelve days before the onset of left hemiplegia, and softening was found in the right temporal lobe at autopsy. Dizziness was observed by both of these patients simultaneously with the onset of the sensory disturbance. In a third case generalized weakness was present for five days. In 2 other cases dizziness alone was the prodrome. In 1 case the patient noted drowsiness for five days, and in 2 cases mental signs were observed; mental confusion was noted for one day in the first case and mental confusion with hallucinations for three weeks in the second case. In the cases of cerebral embolism the symptoms of endocarditis were usually present for varying periods before the onset of signs of cerebral involvement. Five patients complained of headache for from one day to (the intermittent severe type) three years. The patient with severe headache for three years also had dizziness for the same period. Another

patient had dizziness for one day. One patient had a chill ten days post partum, one day before the onset of the signs of cerebral embolism.

Type of Onset.—In the differentiation of cerebral hemorrhage and cerebral thrombosis the type of onset (table 3) is important. In our series the onset with immediate unconsciousness was nearly twice as frequent in cases of hemorrhage as in cases of thrombosis. In the 79 cases in which this point was mentioned the patient was in coma in 50.7 per cent of the cases of cerebral hemorrhage at the onset and in 68.1 per cent of the 116 cases at the time of admission to the hospital. In the cases of cerebral thrombosis, the patient was in coma at the onset in 32.6 per cent of the 49 cases in which this point was recorded and on admission to the hospital in 38.6 per cent of the 101 cases in which this fact was recorded. The onset with convulsions was also more frequent with hemorrhage. In 8 cases of hemorrhage (14.8 per cent of the 54 cases in which this point was noted) a convulsion occurred (jacksonian type in 1) at the onset. In 11 cases (9.5 per cent)

TABLE 3.—*Incidence of Headache, Vomiting, Convulsion and Coma at the Onset of Cerebral Vascular Lesions*

	Headache		Vomiting		Convulsion		Coma	
	At Onset	In Hospital	At Onset	In Hospital	At Onset	In Hospital	At Onset	On Admission
Cerebral hemorrhage..	26	13	19	14	8	11	35	79
Cerebral thrombosis...	3	2	3	2	2	6	16	39
Cerebral embolism.....	6	4	4	2	2	1	5	9

convulsions occurred (jacksonian type in 1) after the patient's admission to the hospital. Of these 11 cases convulsions occurred also at the onset in 3. Therefore, in 16 cases (13.8 per cent) of cerebral hemorrhage convulsions were known to have occurred at the onset of the hemorrhage or after the patient's admission to the hospital. In 8 of these blood was noted in the ventricles, in 2 there was subarachnoid bleeding and in 2 no subarachnoid or ventricular bleeding was seen. This point was not recorded in the 4 remaining cases. The relationship of convulsive seizures to the site of the lesion and to the presence of syphilis is of considerable significance. In 11 of the cases of cerebral hemorrhage with convulsions bleeding occurred in or near the cortex, frontal, parietal or both. In 4 cases the hemorrhage was in the basal ganglions. The remaining case was one of hemorrhage into the left lateral ventricle diffusing into the midbrain. In only 1 of the 16 cases was the presence of syphilis proved; this was in a patient with a hemorrhage into the basal ganglions. The total number of cases of cerebral thrombosis in which convulsions were present at some time during the course of illness was 7, or 6.6 per cent (in 1 case convulsions occurred

with the onset and after the patient's admission to the hospital). Two patients with embolism had convulsions at the onset, and 1 had convulsions at the onset and after being admitted to the hospital. In 4 cases of cerebral thrombosis with convulsions the lesion was in the motor cortex, in 2 in the basal ganglions and in 1, in the pons. Four of the 7 patients had syphilis, 2 with lesions in the motor cortex and 2 with lesions in the basal ganglions. The site of the lesion in the 2 cases of embolism were the cortex of the occipital lobe and the cortex of the parieto-occipital lobes. Neither patient had syphilis.

Broadbent⁶ in 1887 noted that vomiting occurred more frequently with cerebral hemorrhage than with other types of vascular lesion in the brain. Vomiting, if present at the onset and if embolism is excluded, is usually indicative of cerebral hemorrhage. Nineteen patients with cerebral hemorrhage (51.3 per cent of the 37 for whom this point was noted) vomited at the onset. In addition, 6 patients whose history at the onset was unknown vomited during their stay in the hospital. In the group with cerebral thrombosis only 3 patients (6.4 per cent of the 47 for whom this point was noted) vomited at the onset. Another patient in whose case the history of the onset was unknown vomited on admission to the hospital. In these 4 patients the following lesions were observed at autopsy: (1) thrombosis of the basilar artery; (2) softening in the temporal lobe, cerebral edema and nephrosis; (3) thrombosis of the internal carotid artery and peptic ulcer, and (4) thrombosis of the posterior branch of the middle cerebral artery. The lesions in the cases of cerebral embolism with vomiting were multiple emboli of the brain and other organs.

The occurrence of severe headache with the onset of a cerebral vascular lesion is strongly in favor of a diagnosis of cerebral hemorrhage. In 26 cases of cerebral hemorrhage (63.4 per cent of the 41 cases in which this fact was mentioned) there was a complaint of headache at the onset. In addition, 1 patient whose history at the onset is unknown had a headache on admission to the hospital. In the group with cerebral thrombosis (6.1 per cent of the 49 cases in which this symptom was recorded) headache was present in only 3 cases at the onset. One patient whose history at the onset is unknown had a headache on admission to the hospital.

Vital Signs.—The initial temperature, pulse rate and respiratory rate are not of much value in the differentiation of cerebral hemorrhage and cerebral thrombosis. Initial readings of the temperature and pulse rate varied in a rather wide range but were practically the same in both groups. Initial respiratory readings were significant, however, in that the Cheyne-Stokes type of respiration and abnormalities in the depth,

6. Broadbent, W.: *Med.-Chir. Rev.*, 1887, p. 335.

rate and sound of respiration were much more frequent in the patients with cerebral hemorrhage than in the patients with cerebral thrombosis. Thus, 11 cases in which the Cheyne-Stokes type of respiration and 27 cases in which other abnormalities of respiration (stertorous, labored, rapid, dyspneic) were noted (38 cases in all, or 32.7 per cent) were found in the group with cerebral hemorrhage. Among the cases of cerebral thrombosis there were 4 (7 per cent) in which the Cheyne-Stokes type of respiration was noted. In the group with cerebral embolus respiratory abnormalities were noted in 6 cases (Cheyne-Stokes type in 3; rapid in 3, or 26 per cent). A practically constant finding in cases of any type of cerebral vascular lesion was the uniform rise of temperature, pulse rate and respiratory rate several hours or days before death occurred, indicating a collapse of the vasomotor and heat-regulating centers.

Heart.—Clinical abnormalities of the heart were found slightly more frequently in the cases of cerebral thrombosis than in those of cerebral hemorrhage. The heart was rarely normal in cases of cerebral embolism. The heart was clinically enlarged in 84 cases and was fibrillating in 4 other cases of cerebral thrombosis. It was recorded as normal in 18 cases. Cardiac abnormalities occurred in 83 per cent of this group. The heart was clinically enlarged in 66 cases of cerebral hemorrhage and was fibrillating in 2 others and irregular in rhythm in 3. It was recorded as normal in 21 cases. Cardiac abnormalities were noted in 77.1 per cent of this group. In the cases of cerebral embolism the heart was recorded as normal in only 1 instance. Enlargement was recorded in 18 cases and fibrillation in 5 of these 18 (abnormalities in 94.7 per cent).

Arteriosclerosis.—Clinical evidence of arteriosclerosis of the peripheral vessels was noted more frequently in the cases of cerebral thrombosis than in those of cerebral hemorrhage. The incidence of arteriosclerosis in the 69 cases of cerebral hemorrhage in which this point was recorded was as follows: none in 10.1 per cent, moderate in 37.7 per cent, and advanced in 52.2 per cent. In the cases of cerebral thrombosis the peripheral vessels were normal in 1 per cent, moderately sclerotic in 22.3 per cent and markedly sclerotic in 76.7 per cent of the 95 cases in which the point was noted. In the 13 cases of embolism in which the degree of arteriosclerosis was recorded none was noted in 30.7 per cent and it was moderate in 30.7 per cent and advanced in 38.6 per cent.

Blood Pressure.—The comparison of systolic and diastolic blood pressure in our series of cases of cerebral hemorrhage and cerebral thrombosis is given in tables 4 and 5. A glance at the figures in tables 4 and 5 shows that the average systolic and diastolic blood pressure is somewhat higher in persons with cerebral hemorrhage than in those

with cerebral thrombosis. The figures are in number of cases, but they can be used as percentage figures, so closely do the numbers of cases in which the blood pressure was recorded approach 100 (cerebral hemorrhage, 107; cerebral thrombosis, 96).

Eyes.—The type and frequency of pupillary findings in cases of cerebral vascular lesion are moot points, probably because of the changes which occur at various stages of the clinical picture. The findings recorded in table 6 were noted on the first examination at the time of the patient's admission to the hospital. In nearly all the cases this was the only examination of the pupils recorded. In the patients with proved syphilis (of whom there were 15 in the group with hemorrhage, 18

TABLE 4.—*Comparison of the Systolic Blood Pressure in 222 Cases of Cerebral Vascular Lesion*

Systolic Blood Pressure	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
80 to 99.....	1	0	3
100 to 139.....	10	11	6
140 to 159.....	11	17	6
160 to 199.....	42	43	3
200 to 279.....	43	25	1
Total.....	107	96	19

TABLE 5.—*Comparison of the Diastolic Blood Pressure in 222 Cases of Cerebral Vascular Lesion*

Diastolic Blood Pressure	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
40 to 79.....	12	15	8
80 to 99.....	25	31	6
100 to 139.....	58	41	5
140 to 179.....	12	9	..
Total.....	107	96	19

in the group with thrombosis and 1 in the group with embolism) the pupils were of normal size in 16 and small in 3, and contralateral dilatation, homolateral dilatation, inequality, irregularity and large and pinpoint sizes were noted in 1 case each. In 9 cases the size was not recorded. The reaction of the pupils to light in 15 patients with syphilis was normal; in 7 the pupils were fixed to light; in 3 they reacted sluggishly, in 1 they reacted slightly, and in 8 the reaction was not noted.

It is known that advanced age alone affects the size and reaction of the pupils, so we attach no great significance to minor changes in the size and reaction of the pupils of the patients in our series. It is of interest, however, to observe the number of cases in which there was dilatation of the pupil on the side opposite that of the cerebral lesion. It was present in 25.5 per cent of the cases of cerebral hemor-

rhage and in 7.4 per cent of the cases of cerebral thrombosis in which the condition was recorded, exclusive of the cases of proved syphilis (table 6). It is also evident that the total loss of pupillary reaction to light is significant. This occurred in 32.1 per cent of the cases of cerebral hemorrhage and in 9.3 per cent of the cases of cerebral thrombosis (exclusive of the cases of proved syphilis) in which the reaction of the pupils was noted.

Conjugate deviation of the eyes alone or of the head and eyes together occurred in 18 cases of cerebral hemorrhage; in 15 of these the deviation was toward the side of the cerebral lesion and in 3 cases away from it. Conjugate deviation was recorded in 7 cases of cerebral thrombosis; in 6 of these the deviation was toward the side of the cerebral lesion and in 1 case away from it. In 1 case of cerebral embolism deviation was noted toward the side of the cerebral lesion.

TABLE 6.—*Pupillary Size and Reactions in Cases of Cerebral Vascular Lesion**

	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
Size			
Normal.....	23	36	16
Dilated (homolateral).....	2	2	..
Dilated (controlateral).....	22	5	1
Dilated (bilateral).....	4
Small.....	16	8	1
Pinpoint.....	5	3	..
Reaction to Light			
Normal.....	41	45	14
Sluggish.....	12	12	2
Fixed.....	26	6	2
One fixed, one normal.....	2	1	..

* The cases in which syphilis was presented were not included.

Stiffness of the Neck.—Stiffness of the neck is an important differential sign between cerebral hemorrhage and cerebral thrombosis. It was present in 55.1 per cent of the cases of cerebral hemorrhage in which this point was recorded and in only 7 per cent of the cases of cerebral thrombosis. This 7 per cent represents 4 cases, in 1 of which there was evidence of meningeal and vascular syphilis and xanthochromic cerebrospinal fluid. Thrombosis of the internal carotid and middle cerebral arteries on one side was noted at autopsy. In the remaining 3 cases there was high normal or increased pressure in the spinal fluid (from 190 to 240 mm. of water). At autopsy thrombosis of the internal carotid artery was noted in 1 case and in the remaining 2 softenings in the basal ganglions were seen. It is evident that bleeding into the spinal fluid produces meningeal irritation which manifests itself by the usual sign of stiffness of the neck. This is a valuable sign in the differentiation of cerebral hemorrhage and cerebral thrombosis.

Hemiplegia.—In our series left hemiplegia (107 cases) occurred more frequently than right hemiplegia (78 cases). The occurrence of quadriplegia is presumptive evidence of cerebral hemorrhage. Four of the 6 patients with quadriplegia had cerebral hemorrhage, 1 had cerebral thrombosis and 1 cerebral embolism.

Aphasia.—Aphasia was noted in 50 of the 105 patients who were conscious enough for its presence to be determined. Six of these 50 patients had left hemiplegia.

Mental Signs.—Mental signs were slightly more common in the group with cerebral thrombosis than in the group with cerebral hemorrhage (60.3 per cent of 73 cases as compared to 53.6 per cent of 41 cases in which this point was recorded). We did not believe it worth while to correlate the mental signs with the site of the lesion because of complicating factors, for example, cerebral arteriosclerosis. Coma interfered with this determination in 59 cases of cerebral hemorrhage and in 27 cases of cerebral thrombosis.

Plantar Signs.—In the group of cases of cerebral hemorrhage the bilateral occurrence of Babinski's sign was found twice as frequently as in those of cerebral thrombosis. In the cases of cerebral hemorrhage Babinski's sign was noted unilaterally in 40.2 per cent and bilaterally in 27.8 per cent of the 97 cases in which this test was recorded. In the group of cases of cerebral thrombosis the sign was noted unilaterally in 58 per cent and bilaterally in 14.7 per cent of the 88 cases in which the test was recorded.

Progression.—An increase in signs, or signs of progression of the cerebral vascular lesion after the onset, is an important differential point. What is meant by signs of progression can best be illustrated by typical cases.

In case 40 of the cerebral hemorrhage group the patient noted a sudden onset (during excitement) of a "hot feeling" passing over the forehead and behind the eyeballs followed by numbness of the left side of the face and the left upper extremity. The patient felt ill, went outside for air, felt faint and took a taxicab to go home. In the taxicab the patient became nauseated and vomited, and shortly thereafter the left extremities felt stiff. She was carried into her room semi-conscious. The entire episode occupied about one hour.

Case 99 of the cerebral hemorrhage group noted a progression of somewhat longer duration. He experienced a sudden onset of lethargy, loss of energy and frontal headache on the left side, which was continuous. One week later he was seen to carry the left upper extremity in a flexed position, supported by his right hand. It was not known when this weakness occurred. He complained of attacks of numbness in the left extremities. Eight or nine days after the onset his speech became somewhat dysarthric. One day later the left upper extremity became numb, tingled somewhat and twitched occasionally. Immediately thereafter the entire left side became numb. One hour later he was taken to a physician's office.

After leaving the office he became disoriented and lapsed into a semicomatose state. Complete paralysis of the left arm and leg followed shortly thereafter. In this case the period of progression of signs was ten days.

This type of progression of signs is much more often seen in cases of cerebral hemorrhage; progression occurred in 18.7 per cent of the 112 cases in which this point was recorded, as compared with 2 per cent of the cases of cerebral thrombosis. In only 1 case was progression (of one day's duration) noted in the cases of cerebral embolism. The duration of these signs of progression in the cases of hemorrhage was from one-half hour to ten days. In the 2 cases of thrombosis signs of progression lasted for seven hours and two days, respectively. It is not uncommon in cases of lesions of the medulla and pons to note paresthesia ushering in the attack (Merritt and Finland⁷). In only 3 of these 24 cases in which there was progression was the midbrain or pons involved. These signs of progression which develop after the

TABLE 7.—*Length of Survival in 245 Cases of Cerebral Vascular Lesion*

Length of Life After Onset	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
Less than 12 hr.....	5	0	0
12 to 24 hr.....	4	1	0
1 to 4 days.....	48	26	8
5 to 14 days.....	44	35	8
2 wk. to 2 mo.....	13	21	4
2 mo. to 6 mo.....	1	6	1
6 mo. to 7 yr.....	0	7	1
Unknown.....	1	10	1
	116	106	23

onset of the cerebral vascular lesion are not to be confused with premonitory symptoms. The former are severe and are usually localizable to some area in the brain.

Period of Survival.—The length of survival is of importance in the differentiation of cerebral hemorrhage and cerebral thrombosis. In table 7 the length of survival of the patients in our series is indicated.

The shortest periods of survival occurred in the cases of cerebral hemorrhage: One patient lived only three hours after the onset, 2, eight hours, and 2, twelve hours. The longest period of survival in a case of cerebral hemorrhage was eighty-one days. Eighty-seven and eight-tenths per cent of the patients with cerebral hemorrhage died within two weeks. The shortest period of survival in our cases of cerebral thrombosis was twelve hours, the longest, seven years. Sixty-four and five-tenths per cent of the patients with cerebral thrombosis for whom the length of survival was known died within two weeks.

7. Merritt, H. H., and Finland, M.: Vascular Lesions of the Hind-Brain. *Brain* 53:290, 1930.

From observations on this series and from our experience we agree with the numerous authors⁸ who have expressed the belief that death does not occur suddenly (within minutes) after the onset of a cerebral vascular lesion. We also support the statement of Cadwalader^{8b} and of Robinson^{8d} that a cerebral hemorrhage of an appreciable size is probably always fatal.

Urine.—The presence of albumin or casts in the urine was noted in 67.9 per cent of the 78 cases of cerebral hemorrhage in which an examination of the urine was made. This is slightly greater than the 52.7 per cent of the 74 cases of cerebral thrombosis. Sugar was observed in the urine in 10.2 per cent of the 78 cases of cerebral hemorrhage and in 8 per cent of the 94 cases of cerebral thrombosis.

Blood.—A white blood count was made on the patient's admission to the hospital in 165 of the cases of cerebral hemorrhage and cerebral thrombosis. The results varied between 40,000 and 5,000 per cubic millimeter. In 54.6 per cent of the uncomplicated cases of cerebral hemorrhage the count was over 12,000 per cubic millimeter as compared with 10.1 per cent of the cases of cerebral thrombosis with no complications. The highest count in the cases of cerebral thrombosis with no complication was 18,800.

Nonprotein Nitrogen.—The nonprotein nitrogen content of the blood was determined in 107 cases. It was normal in 68 cases, moderately elevated (from 46 to 75 mg.) in 24 cases and markedly elevated (from 76 to 200 mg.) in 9 cases. There was no difference in the incidence of elevation of the nonprotein nitrogen content in the cases of cerebral hemorrhage and that in the cases of cerebral thrombosis.

Glycosuria and Hyperglycemia.—The occurrence of sugar in the urine in patients with a cerebral vascular lesion has been frequently commented on. Sixteen of our patients had glycosuria on admission to the hospital. Only 3 of these patients had a history of diabetes mellitus, and in the majority of the cases subsequent examinations of the urine gave negative results for sugar. Determinations of the sugar content of the blood were made in 40 cases. In 15 cases the sugar

8. (a) Cadwalader, W. B.: A Comparison of the Onset and the Character of the Apoplexy Caused by Cerebral Hemorrhage and by Vascular Occlusion, J. A. M. A. **62**:1385 (May 2) 1914. (b) Moloney, M. F.: Sixty Cases of Sudden or Violent Death, Dublin J. M. Sc., Feb. 1921, p. 68. (c) Oppenheim, H.: Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923, p. 1238. (d) Robinson, G. W.: Encapsulated Brain Hemorrhages, Arch. Neurol. & Psychiat. **27**:1441 (June) 1932. (e) Spiller, W. G.: The Duration of Life After Extensive Hemorrhage of the Brain, J. A. M. A. **51**:2101 (Dec. 19) 1908. (f) Spilsbury, B. H.: Sudden Death, Practitioner **98**:132, 1917. (g) Thomas, H. M., in Osler, William, and McCrae, Thomas: Modern Medicine, Philadelphia, Lea & Febiger, 1915, vol. 5 p. 452. (h) Winkelmann, N. W., and Eckel, J. L.: Extensive Brain Hemorrhage, J. Nerv. & Ment. Dis. **61**:592, 1925.

content of the blood was normal (from 51 to 120 mg. per hundred cubic centimeters). In 9 there was slight hyperglycemia (from 120 to 160 mg.) and in 15 there was moderate or marked hyperglycemia (from 160 to 350 mg.). Two of the patients of this group are known to have diabetes. It is obvious that transient hyperglycemia and glycosuria are not infrequent in patients with a cerebral vascular lesion. It is probably due to a temporary disturbance in the sugar metabolism as a result of the cerebral injury. It is apparently not related to the site of the lesion, but it is noted more frequently in patients with hemorrhage than in those with thrombosis or embolism.

Syphilis in Patients with a Cerebral Vascular Lesion.—Thirty-four of our patients had serologic evidence of a syphilitic infection. The cases were divided as follows: cerebral hemorrhage, 15 cases (positive Wassermann reaction of the blood in 8 cases, of the cerebrospinal fluid in 3 and of both the blood and the cerebrospinal fluid in 4); cerebral thrombosis, 18 cases (positive Wassermann reaction of the blood in

TABLE 8.—*Cerebrospinal Fluid Pressure in 120 Cases of Cerebral Vascular Lesion*

Pressure, Mm. of Fluid	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
Below 200.....	26	38	9
200 to 300.....	12	9	0
301 to 400.....	12	2	1
401 to 1,100.....	11	0	0
Total.....	61	49	10

12 cases, of the cerebrospinal fluid in 2 and of the blood and the cerebrospinal fluid in 4), and cerebral embolus, 1 case (positive reaction of the blood). All the patients with cerebral hemorrhage who gave a positive reaction of the blood had a moderate or marked degree of hypertension. This was not true of the patients with cerebral thrombosis or of the patient with cerebral embolism.

Cerebrospinal Fluid.—A lumbar puncture was performed in 145 of our cases. The observations on the cerebrospinal fluid are important in the differential diagnosis of cerebral hemorrhage and cerebral thrombosis. The pressure and the appearance of the fluid are the two most significant findings. Pressure greater than 400 mm. of cerebrospinal fluid was found only in patients with cerebral hemorrhage, and a frankly bloody fluid is indicative of cerebral hemorrhage. The pressure readings in the 120 cases in which it was recorded are given in table 8.

In 37.7 per cent of our cases of cerebral hemorrhage the pressure was greater than 300 mm. of cerebrospinal fluid, whereas in only 4 per cent of the cases of cerebral thrombosis was such a pressure recorded. In 18 per cent of the cases of cerebral hemorrhage the pressure was greater than 400 mm. Pressure greater than 400 mm. was not recorded

in any case of cerebral thrombosis. This is in agreement with the findings of Krabbe and Geert-Jørgenson.⁹

The appearance of the fluid is very important. A frankly bloody fluid is indicative of cerebral hemorrhage. As shown in table 9, in 74 per cent of the 68 cases of cerebral hemorrhage frankly bloody cerebrospinal fluid was noted. In only 1 of the 64 cases of cerebral thrombosis was bloody fluid noted. There were 7,000 red blood cells per cubic millimeter in this specimen. It was impossible to determine from the records whether the blood in this specimen was due to faulty technic in the performance of the puncture. Examination of the brain at necropsy did not reveal any evidence of blood in the cerebral ventricles or the subarachnoid space. The presence microscopically of a few red blood cells was not uncommon in the cerebrospinal fluid of the patients with cerebral thrombosis, and slight xanthochromia without the presence of blood was noted just as frequently in this group as in the patients with cerebral hemorrhage.

TABLE 9.—*Appearance of the Cerebrospinal Fluid in 145 Cases of Cerebral Vascular Lesion*

Appearance	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism
Bloody.....	49	1	2
Xanthochromic.....	5	6	2
Cloudy.....	1	0	1
Clear.....	13	57	8
Total.....	68	64	13

Two of the patients with cerebral embolism had frankly bloody fluid. This was probably due to the rupture of small mycotic aneurysms.

An analysis of the white cells in the cerebrospinal fluid was of interest in that it revealed that a moderate or marked degree of aseptic meningeal reaction was much more common in the cases of cerebral hemorrhage than in those of cerebral thrombosis. As had been previously pointed out by one of us (H. H. M.¹⁰), this cellular response in the cerebrospinal fluid in patients with cerebral hemorrhage is due to an aseptic meningeal reaction to an area of necrosis near the ventricles. The white cell count in the cerebrospinal fluid in 70 cases of cerebral vascular lesion is given in table 10. Cases in which the cerebrospinal fluid was bloody as well as cases in which the Wassermann reac-

9. Krabbe, K. H., and Geert-Jørgenson, E.: Recherches sur la pression rachidienne et sur le liquide céphalo-rachidien dans les hémorragies et les thromboses du cerveau, *Acta psychiat. et neurol.* **6**:529, 1931.

10. Merritt, H. H., and Moore, M.: Tumours of the Brain Associated with Marked Pleocytosis in the Cerebrospinal Fluid, *J. Neurol. & Psychopath.* **13**:118, 1932.

tion was positive in the blood or cerebrospinal fluid are not included in this table.

In 2 cases of cerebral hemorrhage between 100 and 1,000 white cells per cubic millimeter were present in the cerebrospinal fluid at the first puncture. In 2 other cases subsequent punctures disclosed 1,900 and 3,600 white cells, respectively. In the specimens of fluid with a high white cell count polymorphonuclear leukocytes were the predominating cell type. The occurrence of a large number of white cells is often noted in the cerebrospinal fluid of patients with septic cerebral emboli. This is due to an aseptic meningeal reaction to the septic focus in the brain.

The protein content of the cerebrospinal fluid was usually normal or only moderately elevated in the clear or xanthochromic fluids. A protein content greater than 100 mg. per hundred cubic centimeters occurred in only one specimen of nonbloody fluid (in a case of cerebral

TABLE 10.—*White Blood Cell Count of the Cerebrospinal Fluid in 70 Cases of Cerebral Vascular Lesion**

Cells, per Cu.Mm.	Cerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism	Total
0 to 5.....	9	36	4	49
6 to 10.....	1	2	2	5
11 to 50.....	2	4	2	8
51 to 100.....	0	1	1	2
101 to 1,000.....	2	0	2	4
1,001 to 4,000.....	0	0	2	2
	14	43	18	70

* All cases are excluded in which bloody fluid or positive Wassermann reaction of the blood or cerebrospinal fluid were noted.

thrombosis). The specimens of bloody fluid from patients with cerebral hemorrhage usually had from 200 to 3,000 mg. of protein per hundred cubic centimeters, depending largely on the amount of blood serum present in the cerebrospinal fluid.

The sugar content of the cerebrospinal fluid was determined in 25 cases and was found to be normal or slightly increased. The chloride content was determined in 19 cases and was normal or only slightly decreased in all.

The colloidal gold curve of the cerebrospinal fluid has no differential value in the diagnosis of cerebral vascular lesions. The colloidal gold reaction was tested in 35 of the specimens of fluid from patients with a cerebral hemorrhage. Abnormal curves (first zone, midzone and end-zone curves) were found in the specimens from 21 patients (60 per cent). Three of the 21 patients had a proved syphilis, and a majority of the remainder had bloody cerebrospinal fluid, which would account for the changes in the colloidal gold reaction. Abnormal colloidal gold curves were found in the cerebrospinal fluid of 18 of 45 patients with

cerebral thrombosis. Five of the patients whose colloidal gold curve was abnormal had proved syphilis. There were three normal and three abnormal reactions to the colloidal gold test in specimens of fluid from patients with cerebral embolism.

NECROPSY OBSERVATIONS

Cause of Death.—The cause of death (as determined at autopsy) was as follows: In the group of cases of cerebral hemorrhage death was due to hemorrhage alone in 41 instances. Contributory causes were bronchopneumonia in 45 cases, heart failure in 15, uremia in 5, lobar pneumonia in 3, pulmonary infarct in 3, and diabetes mellitus, lymphoblastoma, vegetative endocarditis and pulmonary tuberculosis in 1 case each. In the cases of cerebral thrombosis the thrombosis alone was the cause of death in 30 instances. Contributory causes were: bronchopneumonia in 41 cases, heart failure in 19, lobar pneumonia in 5, uremia in 3, pulmonary tuberculosis in 2, carcinoma in 2 and pulmonary

TABLE 11.—*Protein Content of the Cerebrospinal Fluid in 53 Cases of Cerebral Hemorrhage and Thrombosis**

Protein Content, Mg. per 100 Cc.	Cerebral Hemorrhage	Cerebral Thrombosis	Total
Under 45.....	5	22	27
46 to 75.....	6	14	20
76 to 100.....	1	4	5
100 to 200.....	0	1	1
	12	41	53

* All cases are excluded in which bloody fluid or a positive Wassermann reaction of the blood or cerebrospinal fluid was noted.

infarct, alcoholism, necrosis of the pancreas and staphylococcic meningitis in 1 each. Cerebral embolism alone was the cause of death in 7 cases. Contributory causes were: vegetative endocarditis in 10 cases, coronary thrombosis in 2 and bronchopneumonia, heart failure, pulmonary infarct and mesenteric thrombosis in 1 each.

Body Build.—The state of nutrition was noted in 111 cases of cerebral hemorrhage. Twenty-seven per cent of the patients were obese, and 16.2 per cent were poorly nourished or emaciated. The remaining 56.8 per cent were well nourished. In the 104 cases of thrombosis in which this condition was recorded 15.2 per cent of the patients were obese, 28 per cent were poorly nourished or emaciated and the remaining 56.8 per cent were normal.

Heart.—The size of the heart was recorded in 99 of the cases of cerebral hemorrhage; there was moderate or marked hypertrophy in 88 per cent. This is in agreement with Herxheimer and Schulz'¹¹

11. Herxheimer, G., and Schulz, K.: Statistisches zum Kapitel Bluthochdruck, Herzhypertrophie, Nierenarteriosklerose, Gehirnblutung nach anatomischen Befunden, Klin. Wchnschr. 10:433, 1933.

figure (91 per cent). The size of the heart was recorded in 87 cases of cerebral thrombosis; enlargement was present in 84 per cent.

Arteriosclerosis.—Examination of the aorta was recorded in 98 cases of cerebral hemorrhage. The aorta was normal in only 9 per cent. It showed evidence of moderate arteriosclerosis in 57 per cent and marked arteriosclerosis in 34 per cent. The condition of the aorta was recorded in 91 cases of cerebral thrombosis. It was normal in 8 per cent, moderately sclerotic in 46 per cent and markedly sclerotic in 42 per cent, and in 4 cases there was syphilitic aortitis.

Coronary sclerosis, moderate or advanced, was present in 61 (73 per cent) of the 84 cases of cerebral hemorrhage in which the condition of the coronary vessels was noted. Coronary sclerosis was found in 81 per cent of the 81 cases of cerebral thrombosis in which the condition of the coronary vessels was noted.

Kidneys.—Gross evidence of lesions in the kidneys was recorded in 42 cases of cerebral hemorrhage (infarcts, 2; chronic nephritis, 15; chronic vascular nephritis, 22, and polycystic kidney, 3), in 40 cases of cerebral thrombosis (infarcts, 2; chronic nephritis, 15; chronic vascular nephritis, 19; polycystic kidney, 1; pyelonephritis, 2, and pyelitis, 1) and in 18 cases of cerebral embolism (infarcts, 16; chronic nephritis, 1, and polycystic kidney, 1).

Cerebral Arteriosclerosis.—Arteriosclerosis of the cerebral vessels was practically a constant finding in the cases of cerebral thrombosis, in contrast to the condition of the vessels in the cases of cerebral hemorrhage, in 21 per cent of which the vessels were normal. Sclerosis of the cerebral vessels in the 81 cases of cerebral hemorrhage in which this point was noted was recorded as follows: advanced sclerosis in 45.7 per cent, and moderate sclerosis in 33.3 per cent. In the remaining 21 per cent the cerebral vessels showed little or no sclerosis (normal). Among the 78 cases of cerebral thrombosis in which this point was recorded, advanced arteriosclerosis was noted in 74.3 per cent and moderate arteriosclerosis in 23 per cent. The patients in the two remaining cases (2.4 per cent) had proved syphilis, and the cerebral vessels were grossly normal at autopsy. In 6.2 per cent (1 case) of the 16 cases of cerebral embolism the cerebral vessels showed advanced sclerosis; in 50 per cent they showed moderate sclerosis, and in the remaining 43.8 per cent they were normal.

Blood in the Ventricles and Subarachnoid Space.—In the 98 cases of cerebral hemorrhage in which this point was recorded blood was present in the cerebral ventricles in 66.3 per cent and in the subarachnoid space in 9.1 per cent. In the remaining 24.6 per cent neither ventricular nor subarachnoid bleeding was noted. In none of the 106 cases of cerebral thrombosis was blood noted in the ventricular or in the subarachnoid

spaces. In the 23 cases of cerebral embolism blood was found in the ventricles in 1 (4.3 per cent) and in the subarachnoid space in 1. In the remaining 91.4 per cent there was no evidence of subarachnoid or ventricular blood.

Location of Lesion.—In the cases of cerebral hemorrhage single lesions were localized as follows: basal ganglions, 58; entire hemisphere, 6; frontal lobe, 13; parietal lobe, 3; temporal lobe, 9; occipital lobe, 5; ventricle, 1; brain stem, 1; midbrain, 3, and cerebellum, 2.

In the remaining 12 cases (10.3 per cent) there were multiple discrete lesions. In 4 cases each there were 2 cerebral hemorrhages (right half of the cerebellum and left occipital region; right temporal and left occipital area; left basal ganglions and right frontal region, and basal ganglions on both sides). In 7 cases there were hemorrhage and softening (hemorrhage in the right basal ganglions and softening of the left occipital lobe, 2 cases; hemorrhage in the right basal ganglions and softening of the right insula; hemorrhage in the right occipital region and softening of the right internal capsule; hemorrhage in the right side of the pons and softening of the right parietal lobe; hemorrhage in the left basal ganglions and softening of the left external capsule; hemorrhage in the left basal ganglions and softening of the right basal ganglions). In the remaining case hemorrhage occurred into the right basal ganglions and into the pons, and there was softening of the left basal ganglions. In 3 cases the location of the lesion was not recorded.

Single lesions in the cases of cerebral thrombosis were localized as follows: basal ganglions, 38; frontal lobe, 3; parietal lobe, 4; temporal lobe, 6; occipital lobe, 5; brain stem, 3; cerebellum, 2, and midbrain, 1.

In 24 cases (27 per cent) multiple softenings were present, while in the remaining 18 cases there was thrombosis of one or more of the large cerebral vessels, with extensive areas of softening. In 2 cases the location of the lesion was not recorded.

Multiple lesions were the rule in cases of cerebral embolism. In all but 6 of the 23 cases in our series multiple lesions were present (73.9 per cent). In 3 cases these included occlusion of a large cerebral vessel (the basilar artery in 2 cases and the right anterior cerebral artery in 1). In 21 of the cases of cerebral embolism infarcts were present in other viscera, and in the remaining 2 there were vegetative endocarditis with multiple infarcts in the brain.

FREQUENCY OF CEREBRAL VASCULAR LESIONS

Lest the distribution (116 cases of hemorrhage, 106 of thrombosis and 23 of embolism) in our series of cases of cerebral vascular lesions prove misleading, we wish to note what we believe to be a more accurate incidence. We have critically studied the records of cases of cerebral

vascular lesions observed at the Boston City Hospital within the past five years, in many of which the patients were examined by us. These include only those cases in which the diagnosis was reasonably certain, and among them are some of the cases included in our series. Cases are not included unless a lumbar puncture was performed. The cases which we were able to accept for this group (to give us an index of distribution) total 407. The diagnosis of cerebral thrombosis was made in 81.8 per cent of these cases, of cerebral hemorrhage in 15 per cent and of cerebral embolism in the remaining 3.2 per cent. We feel that this is the more probable ratio of incidence of these three types of cerebral vascular lesion. A series controlled by observations at necropsy gives a false ratio between the incidence of cerebral hemorrhage and cerebral thrombosis because a great majority of patients with the latter condition recover to a degree sufficient for discharge from the hospital.

SUMMARY

The use of hospital records of patients admitted with cerebral vascular lesion which cause a fatal outcome in obtaining conclusions has its limitations, chiefly because of the selective nature of the material. Such a selection of cases proved at necropsy is necessary in any attempt to determine the findings which are of value in a differential diagnosis. We have used the records of 245 cases of cerebral vascular lesion as a basis for this study. All of these cases were studied clinically and at necropsy. We have slighted the analysis of the cases of cerebral embolism chiefly because of the few cases and also because of the relative ease with which this diagnosis is made.

1. The average age of the patients with cerebral hemorrhage is slightly lower than that of patients with cerebral thrombosis. Cerebral vascular accidents are rare below the age of 40, but cerebral hemorrhage occurs more frequently in the decade from 40 to 50 than cerebral thrombosis.

2. The symptoms occurring at the onset of the lesion are of considerable aid in the differential diagnosis.

The occurrence of a sudden severe headache or vomiting at the onset is strongly in favor of a diagnosis of cerebral hemorrhage.

Convulsions are more frequent in the cases of cerebral hemorrhage. In our series they occurred in 13.8 per cent of the cases of cerebral hemorrhage and in 6.6 per cent of the cases of cerebral thrombosis. The convulsions which occurred in cases of cerebral thrombosis were usually associated with syphilis or a lesion in the motor cortex.

The onset with immediate unconsciousness is more frequent in cases of cerebral hemorrhage (51 per cent) than in cases of cerebral thrombosis (32 per cent). The presence of coma on the patient's admission

to the hospital is probably a more reliable index to the relative frequency of this symptom (cerebral hemorrhage, 68 per cent; cerebral thrombosis, 39 per cent).

Signs of progression of the cerebral vascular lesion after the onset are more frequent in the cases of cerebral hemorrhage.

3. Abnormalities in the depth, rate, rhythm and sound of the respirations are more frequent in cases of cerebral hemorrhage.

4. The blood pressure ranged somewhat higher in our cases of cerebral hemorrhage. The systolic blood pressure was greater than 200 mm. in 41 per cent of the cases of cerebral hemorrhage, as compared with 26 per cent of the cases of cerebral thrombosis. Cerebral hemorrhage or cerebral thrombosis is not rare in a patient with normal blood pressure.

5. Arteriosclerosis as evidenced by examination of the peripheral vessels and those of the retina occurs more frequently and is more advanced in cases of cerebral thrombosis. There was no evidence of arteriosclerosis in 10 per cent of our cases of cerebral hemorrhage, as compared with 1 per cent of the cases of cerebral thrombosis.

6. Abnormalities in the eyes are found more frequently in cases of cerebral hemorrhage. Conjugate deviation of the eyes (or head and eyes) was found in 15 per cent of our cases of cerebral hemorrhage and in 7 per cent of the cases of cerebral thrombosis. Unilateral dilatation of the pupils (usually on the side opposite the cerebral lesion) occurred in 25 per cent of the cases of cerebral hemorrhage, as compared with 7.4 per cent of the cases of cerebral thrombosis. Total loss of the pupillary light reflex was noted in 32 per cent of the cases of cerebral hemorrhage and in 9 per cent of the cases of cerebral thrombosis. Cases in which the presence of syphilis was proved were excluded from this calculation.

7. Stiffness of the neck is usually indicative of a cerebral hemorrhage. It was found in 55 per cent of the cases of cerebral hemorrhage and in only 7 per cent of the cases of cerebral thrombosis.

8. The bilateral occurrence of the Babinski sign was noted almost twice as often in the cases of cerebral hemorrhage (28 per cent) as in the cases of cerebral thrombosis (15 per cent).

9. The initial leukocyte count in cases of cerebral hemorrhage with no complications is often very high. The count was markedly increased in 55 per cent of our cases of cerebral hemorrhage, as compared with 10 per cent of our cases of cerebral thrombosis with no complications.

10. The findings at lumbar puncture are of great aid in the differential diagnosis between cerebral hemorrhage and cerebral thrombosis. The cerebrospinal fluid pressure was increased in 57 per cent of our cases of

cerebral hemorrhage and in 22 per cent of the cases of cerebral thrombosis. In 38 per cent of the cases of cerebral hemorrhage the cerebrospinal fluid pressure was greater than 300 mm., and in 18 per cent the pressure was greater than 400 mm. In the cases of cerebral thrombosis a pressure greater than 300 mm. was rare and pressure greater than 400 mm. did not occur.

A grossly bloody fluid was found in 74 per cent of the cases of cerebral hemorrhage, and it was rarely, if ever, found in cases of cerebral thrombosis.

11. The period of survival is usually shorter in cases of cerebral hemorrhage than in those of cerebral thrombosis. In 50 per cent of the cases of cerebral hemorrhage the patient died within four days of onset, and in only 28 per cent of the cases of cerebral thrombosis did the patient die in this period. Cerebral vascular lesions do not cause sudden death.

CONCLUSION

The differential diagnosis between cerebral hemorrhage and cerebral thrombosis can usually be made during life. A carefully taken history of the onset and progress is of paramount importance. A thorough analysis of the history, together with the results of the physical and neurologic examinations and of the examination of the cerebrospinal fluid, should make the differentiation possible in nearly 100 per cent of the cases.

PATHOLOGY OF THE VESSELS OF THE PULMONARY CIRCULATION

PART II

O. BRENNER, M.D., M.R.C.P.

Physician for Outpatients and Physician in Charge of the Cardiographic
Department, Queen's Hospital
BIRMINGHAM, ENGLAND

DISEASES OF THE PULMONARY VESSELS

HISTORY

Excellent historical accounts have been given by Costa,⁶³ Giroux,¹¹⁴ Posselt²⁴⁰ and others, so a brief sketch will suffice here.

Pulmonary arteriosclerosis was recognized early in the last century by Brisson (1803), Andral (1829), Lobstein (1835) and others, but it was thought to be rare. Dietrich (1850) first recognized its frequency in cases of mitral stenosis and emphysema. Posselt²⁴⁰ collected all the reports of cases (274) published in the nineteenth century and showed that in 40 per cent of the cases mitral stenosis was present and that in the great majority of the rest there were various other types of heart disease. Emphysema, he thought, was not a cause. The chief cause was a high pulmonary arterial pressure, though infections, intoxications and congenital inferiority of the pulmonary arteries also played a part. In 1908 he²³⁹ described, on the basis of 10 of his own cases, the clinical picture that he thought was characteristic of pulmonary arteriosclerosis. Comparatively little has been added to the accepted symptomatology since.

In the present century new forms of disease of the pulmonary arteries have been differentiated. "Primary pulmonary arteriosclerosis," in which no obvious cause for the sclerosis can be found, has been separated from the main group of "secondary pulmonary sclerosis," in which there is some obvious cardiac or vascular cause for the increased pulmonary arterial blood pressure. Interest in primary sclerosis was first aroused by the reports of Romberg (1891) and Aust (1892), though cases possibly of this type had been described by Klob (1865), Crudeli (1868) and Wolfram (1883). Many cases have been reported since, though in most of them the correctness of the diagnosis is doubtful.

In this series of five papers the superior numbers refer to the bibliography which will be published in connection with the last paper. The superior letters refer to footnotes.

Since several types of lesions are found in the pulmonary vessels, it is probable that it will be necessary to subdivide the cases of primary sclerosis.

The concept of "Ayerza's disease," elaborated by the Argentinian school, has attracted a great deal of notice. The meaning of the term "Ayerza's disease" varies with each author who uses it. Generally it signifies a condition in which the patient has heart failure with intense cyanosis and at autopsy is found to have syphilis of the pulmonary arteries and possibly also of the lungs and bronchi. Reasons will be given later in the appropriate section for doubting the specificity of this syndrome.

It has long been known that subacute bacterial endarteritis may attack the pulmonary arteries in cases of congenital heart disease, especially when there is a patent ductus arteriosus. In 1917 Lutembacher¹⁶³ described acute, subacute or chronic endarteritis of large and medium-sized branches of the pulmonary artery in cases of mitral stenosis and held this responsible for the fever and rapid downhill course in some cases. This process, together with infection of the edematous fluid in the pulmonary alveoli, has been thought⁵² to be responsible for the pyrexial attacks in patients with congestive heart failure. Pappenheimer (1924), Kugel (1928), Chiari (1930) and others have shown that rheumatic fever may injure both large and small branches of the pulmonary artery. Laubry and Thomas (1925, 1926, 1927) and many others have insisted on the importance and frequency of syphilis of the pulmonary arteries. The frequency of thrombosis of the pulmonary arteries, often with little apparent embarrassment of the circulation, has been stressed by Billings (1921), Møller (1922), Brenner (1931) and others. Laubry (1922) reported cases which he thought demonstrated the importance of compression of the pulmonary artery, e. g., by enlarged mediastinal glands, in the production of failure of the right heart.

It is thus clear that a great variety of lesions of the pulmonary artery are now recognized and that several different symptom complexes are with more or less justification ascribed to them.

SCHEME OF THE PRESENT INVESTIGATION

Most of the large number of papers on diseases of the pulmonary vessels have consisted of reports of single cases, without controls, from which sweeping conclusions have often unjustifiably been drawn. Steinberg²⁸⁴ made macroscopic observations on the pulmonary arteries in 500 consecutive autopsies, but a study of this type is inadequate as many lesions even in the larger branches are missed and the small vessels cannot be examined except microscopically. Costa⁸ studied the pul-

monary vessels microscopically in 210 unselected autopsies, but he was interested only in arteriosclerosis and his attention was fixed especially on the stem of the pulmonary artery and its larger branches. Ljungdahl¹⁷⁶ considered the question only from the standpoint of the incidence of pulmonary arteriosclerosis in various types of cardiac and pulmonary disease. It was felt that before all this mass of accumulated data could be of use it was necessary to provide a background of carefully controlled observations. The study here reported was undertaken as a contribution toward that end.

In 100 consecutive unselected autopsies a careful macroscopic examination was made of the main extrapulmonary pulmonary arteries and veins and of the pulmonary arterial branches as far as they could be opened up with fine scissors. The circumference of the stem of the pulmonary arteries was measured 2 cm. above the cusps and compared with that of the aorta. The circumference of the right and left arteries at the hilus and of the pulmonary veins at their junction with the left auricle was also measured.

Microscopic sections of all portions of the pulmonary vascular bed were examined, namely, transverse sections of the stem of the pulmonary artery 2 cm. above the cusps; longitudinal sections of the root of the stem, including the pulmonary valve and a portion of the right ventricle; transverse sections of the main extrapulmonary arteries and of the main extrapulmonary veins just proximal to their junction with the left auricle; the large elastic intrapulmonary arteries; and the small muscular arteries, arterioles, venules, capillaries and veins of all sizes. For the examination of the intrapulmonary vessels sections were taken from all the lobes of each lung and usually both from near the hilus and from the periphery so as to insure obtaining both large and small vessels. The sections were stained by each of the following methods: (1) methylene blue and eosin, (2) Mallory's phosphotungstic hematoxylin, (3) Mallory's connective tissue stain and (4) Verhoeff's elastic tissue stain and Van Gieson's stain. The thickness of each of the three coats of the extrapulmonary vessels was measured by means of an ocular micrometer. Many of the intrapulmonary vessels in each of the categories previously mentioned were examined and measured. Records were made of any pathologic changes, together with the external diameter of the vessel, the diameter of its lumen and the thickness of each of its coats. The pathologic changes in the pulmonary vessels were correlated with those in the other organs, particularly the heart and lungs, and with those in the systemic vessels, studied by means of sections of the organs stained with methylene blue and eosin and with Van Gieson's stain and Verhoeff's elastic tissue stain. The symptoms presented during life, as recorded in the case report, were compared with

the pathologic findings. This was the least satisfactory portion of the investigation, since the clinical findings had been recorded by different observers with varying degrees of care and accuracy, and often information on important points was missing.

Classification.—A surprisingly large number of different pathologic processes were found in the pulmonary vessels in the course of the investigation. They may be classified as follows (each type of lesion will be considered in turn, irrespective of what part of the pulmonary vascular bed is involved, though for the sake of clarity they are here classified by site as well as by pathologic type) :

DISEASES OF THE ARTERIES

1. Arteriosclerosis: (a) secondary, (b) primary
2. "Endarteritis obliterans"
3. Proliferation of the elastica interna
4. Endothelial proliferation
5. Hypertrophy of the media
6. Fibrosis of the media
7. Syphilis of the pulmonary arteries
8. Ayerza's disease
9. Tubercle of the pulmonary arteries
10. Rheumatism of the pulmonary arteries
11. Acute septic arteritis.
12. Neoplasm
13. Thrombosis and embolism
14. Aneurysm

DISEASES OF THE ARTERIOLES AND VENULES

1. Sclerosis
2. Endothelial proliferation
3. Infections, acute and chronic
4. Neoplasm
5. Thrombosis

DISEASES OF THE VEINS

1. Sclerosis
2. Infections, acute and chronic
3. Neoplasm
4. Thrombosis

SECONDARY PULMONARY VASCULAR ARTERIOSCLEROSIS

Sclerosis of the pulmonary arteries is usually subdivided into primary and secondary types. In the primary type none of the conditions, such as mitral stenosis or chronic pulmonary disease, which are generally thought to cause a rise in the pulmonary arterial pressure, is present and there is an otherwise unexplained hypertrophy of the right ventricle. In secondary sclerosis one or more of the conditions that are thought to be capable of raising the pulmonary arterial pressure are present or, if they are absent, there is no hypertrophy of the right ventricle. Most of the cases of senile pulmonary arteriosclerosis fall into the group in which there is no obvious cause for a rise in the pulmonary arterial pressure but in which there is no hypertrophy of the right ventricle. No place has been found for this large group in previous definitions, or else the definitions have been so faulty that these cases should logically have been included in the category of primary sclerosis.

CLASSIFICATION OF THE CONDITIONS

Since chronic diseases of the heart and lung have usually been stated to be the chief causes of secondary sclerosis the 100 cases in the present series have been divided into eight groups according to the presence or absence of these factors:

1. The "no cause" group (31 cases), in which none of these factors was present though in 12 cases pleural adhesions were present, and in one of these one pleural cavity was obliterated, the other being normal.

2. The "pulmonary disease" group (29 cases), in which chronic disease of the lung was present: 16 cases of emphysema, 3 of emphysema with fibrosis of the lungs, 2 of bronchiectasis, 3 of fibrocaseous tuberculosis, 2 of tuberculosis with emphysema, 2 of chronic abscess of the lung and 1 of neoplasm.

3. The cardiac disease group (7 cases), in which cardiac disease alone was present: 5 cases of disease of the coronary artery with cardiac hypertrophy, 1 case of rheumatic mitral and aortic disease and 1 of hypertrophy of unknown origin in a boy aged 16 years.

4. The hypertension group (9 cases), in which essential hypertension or chronic glomerulonephritis with hypertension was present.

5. The "cardiac and pulmonary disease" group (13 cases), in which both chronic cardiac and chronic pulmonary disease were present: 5 cases of disease of the coronary artery with cardiac hypertrophy and emphysema, sometimes also with pulmonary fibrosis; 3 of rheumatic heart disease (including 1 case that was complicated by infective endocarditis), with emphysema or pulmonary fibrosis; 3 of syphilitic aortitis with pulmonary fibrosis (in 1 case with bronchiectasis and in another

case with fibrocaseous tuberculosis); 1 of aortic stenosis (? arteriosclerotic) with emphysema and pulmonary fibrosis, and 1 of pericarditis with emphysema.

6. "Cardiac disease and hypertension" group (3 cases) in which there was independent cardiac disease (sclerosis of the coronary artery with cardiac hypertrophy and in 2 cases occlusion of the coronary artery with myocardial infarction) in addition to hypertension.

7. "Cardiac and pulmonary disease and hypertension" group (3 cases), in which all 3 factors were present. In addition to hypertension in 1 case there was syphilitic aortitis and emphysema, and in 2 cases sclerosis of the coronary artery with emphysema.

8. "Pulmonary disease and hypertension" group (5 cases), in which there was chronic pulmonary disease (3 cases of emphysema, 1 case of emphysema with pulmonary fibrosis, and 1 of fibrocaseous tuberculosis with emphysema) as well as hypertension.

INCIDENCE

In the few systematic inquiries into pulmonary arteriosclerosis that have been made, estimates of its frequency have varied widely for three main reasons: 1. For some papers^h the statistics were obtained from routine autopsy protocols, in which usually only extreme pulmonary vascular sclerosis is noted. It is rare in routine autopsies for the pulmonary vessels to be carefully examined, and unless specially looked for, most cases will be missed. Miller²⁰³ found an incidence of pulmonary arteriosclerosis of 7.4 per cent in 800 routine autopsies and Moschowitz,²¹³ 6.5 per cent in 770 cases. Both these figures are much too low. 2. Sclerosis of the small vessels can be detected only microscopically, and even in the large vessels marked diffuse intimal thickening may easily be missed by the naked eye. Costa⁶³ noted sclerosis in the stem of the pulmonary artery macroscopically in only 8 per cent of 210 cases and microscopically in 65 per cent of the same cases. Not all authors have agreed as to what constitutes arteriosclerosis. Giroux¹¹⁴ excluded cases in which there were only a few fatty patches or streaks in the intima, the rest of the intima appearing normally thin and translucent. But on microscopic study the normal-looking intima is often found to be considerably thickened. These changes undoubtedly represent mild or moderate grades of arteriosclerosis, and there is no logical reason for excluding them.

Of the 100 cases in the present series 59 were in males and 41 in females. Macroscopic evidence of sclerosis was present in 68 (41

(h) 203, 213.

males, or 70 per cent, and 27 females, or 66 per cent). The only available comparable statistics are those of Steinberg,²⁸⁴ who on careful macroscopic examination of the pulmonary arteries in 500 unselected autopsies observed sclerosis in 65 per cent. In his series, as in the present one, males and females were affected in equal numbers.

In the present series, on microscopic examination, in only 3 cases (all in children under 10 years of age) were no sclerotic changes noted in any part of the pulmonary vascular bed. Thus, sclerotic changes (often slight) were seen in some part of the pulmonary vascular bed in 97 per cent of an unselected consecutive series of autopsies. This fact robs the observation of sclerotic changes in the pulmonary vessels of much of the significance that has heretofore been attributed to it. Sclerosis was observed as common in the pulmonary as in the systemic circulation (though less severe usually), and there is no reason to believe that it is more important. Indeed, since the lungs are less vulnerable than the heart or brain and since destruction of large portions of the lung may occur without endangering life, it is probably of less importance.

No comparable figures as to the frequency of pulmonary vascular sclerosis as observed on microscopic examination are available in the literature.

GROSS APPEARANCE

The macroscopic appearances in cases of secondary pulmonary arteriosclerosis differ from those of sclerosis of the systemic vessels only in usually being less severe.

(a) *Dilatation*.—The stem and branches of a sclerosed pulmonary artery are usually dilated.¹ In the present series in the 15 cases in adults in which no macroscopic evidence of sclerosis was found (slight microscopic sclerosis was present in all but 1 case) and in which there was none of the diseases thought to be capable of raising the pulmonary arterial pressure, the circumference of the stem of the pulmonary artery 2 cm. above the cusps ranged from 5.8 to 8.3 cm., except in 1 case, in which it was 9.3 cm., and that of the main branches at the hilus of the lung varied from 3.8 to 4.8 cm., except in one case, in which it was 5.1 cm. The pulmonary arteries have, therefore, been considered to be dilated if the circumference of the stem exceeded 8.5 cm. or if that of the main branches at the hilus exceeded 5 cm. Table 1 shows the distribution and severity of the dilatation in the 100 cases graded according to the severity of the sclerosis noted macroscopically. The manner in which the severity of the sclerosis was graded will be described presently. It is clear that in the present series the dilatation of the

(i) 78, 92, 114, 136, 160, 167, 174, 183, 186, 193, 204, 250, 273, 274, 308, 331.

TABLE 1.—Incidence of Dilatation of the Pulmonary Arteries in Adults Over 20 with Pulmonary Vascular Sclerosis

De- gree of Sele- rosi	Males												Females																	
	Dilatation of Stem and at Hilus												Dilatation of Stem and at Hilus																	
	Circumference of Stem, Cm.				Hilus, Cm.				Dilatation at Hilus				Circumference of Stem, Cm.				Hilus, Cm.				Dilatation at Hilus									
	No. Cases	Mini- num	Maxi- num	Aver- age	No. Cases	Mini- num	Maxi- num	Aver- age	No. Cases	Per- cent.	No. Cases	Per- cent.	No. Cases	Per- cent.	No. Cases	Mini- num	Maxi- num	Aver- age	No. Cases	Per- cent.	No. Cases	Mini- num	Maxi- num	Aver- age	No. Cases	Per- cent.	No. Cases			
0	9	7.2	9.4	7.9	3.8	5.1	4.4	1	11	1	11	1	11	3	33	10	5.8	10.3	4.5	3.8	7.5	4.8	1	10	1	10	
+	13	6.8	9.2	8.0	3.0	7.3	5.1	2	15	1	8	2	15	5	39	14	5.9	8.5	7.2	3.7	5.5	4.5	3	21	1	7	..	4	20	
++	15	6.9	10.3	8.4	4.7	5.9	5.4	3	20	3	20	4	27	10	67	7	6.6	9.0	8.4	3.8	6.0	4.9	3	43	1	14	2	28	6	85
+++	10	6.8	10.2	8.1	4.7	7.5	5.5	2	20	4	40	6	60	4	7.3	8.9	8.2	5.1	7.0	5.8	2	50	2	50	4	100
++++	0	1	9.0	5.5	1	1	..

pulmonary artery was much commoner in cases of sclerosis, particularly of the severer grades, than in those in which sclerosis was not present. The greater frequency of dilatation in the males with no, or slight, sclerosis was perhaps due to the fact that the same upper limit for the normal was taken for both sexes, whereas the average circumference for normal women is distinctly less than that for normal men. There were relatively more cases of the higher grades of sclerosis in the more advanced age groups, and it is possible that the greater prevalence of dilatation in those groups may have been due to this; but the number of cases in which there was no sclerosis in the older age groups was too small for this factor to be controlled.

Dilatation may be the only macroscopic sign of pulmonary vascular sclerosis. In the case of a woman in whom the vessels were apparently normal, except that the circumference of the stem of the pulmonary artery was 9.3 cm., fairly marked sclerosis was seen microscopically. The same was true in two of Schreyer's cases.²⁷⁴

It is probable that during life the circumference of the pulmonary vessels is greater than at autopsy, and it is possible that during life the circumference of the normal vessels may be as great as that of those that are apparently dilated at autopsy. If this is so, the "dilatation" is really a measure of the lack of elasticity of the vessels. The post-mortem "dilatation" in either event indicates an abnormal condition of the vessels.

(b) *Atherosclerosis*.—Small, irregular, whitish or yellow patches or streaks elongated in the direction of the blood stream are present in the intima of the affected vessels. In the slighter grades they are not raised above the surface, but in severer cases they may be raised considerably. The patches are commonest and largest near the mouths of branches. Calcification is rare and is usually noted only on microscopic examination, but occasionally ²⁶² it is seen macroscopically. Atheromatous ulcers are rare and have been reported only by Hornowski.¹³⁶ In the most severe cases the plaques may be almost confluent in some places. In the extrapulmonary and larger intrapulmonary arteries the intima between the patches often seems thickened and opaque, but in the smaller arteries, except in the most marked cases, it seems normally thin and translucent. In a few of the most severe cases in the present series the thickened intima looked wrinkled, owing, as shown microscopically, to the presence of deep furrows in the otherwise uniformly thickened intima. In a few cases the stem and extrapulmonary branches were thick and heavy, owing to thickening of the media. Usually in severe cases the smaller intrapulmonary branches were thickened and rigid, and their wide gaping mouths were unusually prominent on the cut surface of the lung.

In the present series the severity of the macroscopic changes has arbitrarily been graded from +, when there were only a few isolated fatty patches, to + + + +, when practically no normal intima could be found in any branch that could be opened up with fine scissors. The distribution of the cases according to the severity of the macroscopic sclerosis in males and females is shown in table 2. Though the incidence of sclerosis is approximately equal in the two sexes, there is a slight preponderance of the more severe grades of sclerosis in males. Steinberg,²⁸⁴ who graded his cases similarly, graded 37 per cent of his cases +, 24 per cent + +, 10 per cent + + + and 3 per cent + + + +, figures which compare fairly closely with those in table 2.

(c) *Distribution of Sclerosis.*—The changes are least marked in the stem of the pulmonary artery and its extrapulmonary branches, a fact which accounts for the common underestimation of the frequency of

TABLE 2.—*Degree of Gross Vascular Sclerosis in Males and Females*

Degree of Sclerosis	Males		Females		Total Percentage
	Number	Percentage	Number	Percentage	
0	18	31	14	34	32
+	13	22	15	37	28
++	17	29	6	15	23
+++	11	19	5	12	16
++++	1	2	1

pulmonary arteriosclerosis. Sclerosis in the stem is commonest just before the bifurcation and immediately above the cusps, which occasionally are involved at their commissures, so that the cusps may adhere slightly to each other and to the arterial wall. A similar but much more severe process causes arteriosclerotic aortic stenosis, but in the pulmonary artery the changes are minimal, and no case of arteriosclerotic stenosis of the pulmonary valve has been reported. The changes usually increase at the hilus of the lung. They sometimes reach their maximum in the main intrapulmonary branches and rapidly diminish in the smaller arteries, even in cases in which the microscope shows extensive lesions in the smallest vessels. In other cases the sclerosis extends into the smallest vessels that can be traced with the naked eye.

Laubry¹⁵⁸ said that in cases of chronic disease of the lung sclerosis is confined to the large branches, while in cases of heart disease all the branches down to the smallest that can be traced are involved. However, many cases of pulmonary disease have been reported in which the sclerosis extended to the finest traceable vessels,¹ and fewer cases have

(j) 92, 186, 193, 250, 262.

been reported in which there was sclerosis only of the large branches,^k while in cases of heart disease sometimes the medium-sized vessels are said to be chiefly involved²⁵² and sometimes the large vessels^l but usually all the branches down to the finest.^m

Table 3 shows the distribution of macroscopic sclerosis in the present series in the various etiologic groups as defined previously. Macroscopic sclerosis of the large vessels alone was commoner than sclerosis of both large and small vessels, and there was no significant difference in the distribution in the various etiologic groups. In cases of congestive heart failure, however, the small vessels were more commonly involved. It should be stressed that the vessels here called small were all more than 1 mm. in external diameter and they were all histologically classed as "large elastic arteries." The distribution of the gross changes is not

TABLE 3.—*Distribution of Gross Sclerosis in the Pulmonary Arteries*

Etiologic Groups	Patients with Sclerosis in Large Arteries Only	Patients with Sclerosis in Large and Small Arteries
No case	10	3†
Pulmonary disease	18	6
Cardiac disease	3	2
Hypertension	5	..
Pulmonary and cardiac disease.....	8	3
Cardiac disease and hypertension.....	2	..
Pulmonary and cardiac disease and hypertension.....	1	1
Pulmonary disease and hypertension.....	3	2
Congestive heart failure*.....	8	6

* The cases of congestive heart failure are all included in one or the other of the eight etiologic groups.

† Including 1 patient with primary sclerosis.

necessarily related to the distribution of the microscopic changes in the small muscular arteries, arterioles and venules.

Table 4 shows that macroscopic sclerosis increased in frequency with age in both sexes. Of 30 patients under 40, 8 (27 per cent) showed sclerosis, while of 70 patients over 40, 60 (86 per cent) showed sclerosis. The influence of the factors thought capable of raising the pulmonary arterial pressure must be excluded before the effect of age can be evaluated. Table 5 shows that of the 31 patients in whom no such factor was present 16 were under and 15 over 40. Excluding 1 patient with primary pulmonary arteriosclerosis who was under 40, only 1 of the 15 patients under 40 (7 per cent) and 12 of the 15 over 40 (80 per cent) showed macroscopic sclerosis. Thus, the incidence of macroscopic pulmonary arteriosclerosis increased with the age of the patients even in the absence of factors commonly thought to raise the pulmonary

(k) 202, 204.

(l) 176, 335.

(m) 52, 78, 162, 273, 276, 306, 335.

arterial pressure. Ljungdahl¹⁷⁶ observed gross pulmonary arteriosclerosis in 50 per cent of 52 persons over 50 with no factor present which was thought likely to have raised the pulmonary arterial pressure. Othersⁿ have said that slight sclerosis is common in the aged, but no statistics have been given. Fischer¹⁰³ agreed, but attributed the increase to the presence of senile emphysema (which was excluded in the cases in the "no cause" group in the present series). Moschowitz^o stated that decrescent pulmonary arteriosclerosis is rare until the patients are well on in senility. This conclusion was probably reached because no special search for pulmonary arteriosclerosis was made. Costa⁶³ said that although microscopic sclerosis of the stem of the pulmonary artery is almost always present in patients over 60, the gross changes are rare. However, the gross changes are always least in the stem of the pulmonary artery. Thus, nothing in the literature invalidates the

TABLE 4.—*Distribution of Gross Sclerosis According to Age and Sex*

Age, Years	Males		Females	
	No. of Patients	No. of Patients with Sclerosis	No. of Patients	No. of Patients with Sclerosis
0-9.....	2	0	3	0
10-19.....	9	1
20-29.....	3	2	2	1
30-39.....	5	3	6	1
40-49.....	10	6	3	2
50-59.....	14	14	9	6
60-69.....	12	12	8	7
70-79.....	4	3	8	8
80-89.....	2	2

conclusion that gross pulmonary arteriosclerosis is increasingly common with an increase in age, even in the absence of any evidence of a raised pulmonary arterial pressure.

Table 5 shows that in the presence of disease of the heart or lung, separately or together, the incidence of gross sclerosis is somewhat increased in patients under 40, but not significantly in those over 40, though after the age of 40 the severity of the sclerosis is increased.

MICROSCOPIC CHANGES

The smallest arteries that can be opened and examined macroscopically are from 1 to 2 mm. in diameter and are classed microscopically as large arteries. Macroscopic inspection gives no information about the small arteries, and even in the large vessels the microscope often reveals unsuspected lesions. Microscopic sclerosis may involve vessels of all sizes, from the stem of the pulmonary artery

(n) 150, 284, 295.

(o) 212, 213.

to the arterioles, and from the venules to the main veins. The appearances vary somewhat in different situations.

Method of Grading the Lesions.—It was felt that some numerical method of grading the lesions was desirable. It is obvious that any method must be rough and that no statistical accuracy can be claimed. The figures given in the following tables are intended merely as a rough indication of the differences in the severity of the lesions in the different groups of cases. In every case the severity of the lesions in each type of vessel (stem of the pulmonary artery, large elastic arteries, muscular arteries and so forth) was graded from 0 to + + + +, according to the criteria given for each type of vessel.

TABLE 5.—*Distribution of Gross Pulmonary Arteriosclerosis According to Age and Etiologic Factor*

Etiologic Factor	Patients Aged 0 to 39 Years				Patients Aged 40 to 89 Years			
	No. of Pa- tients	Patients with Sclerosis		Average Degree of Sclerosis†	No. of Pa- tients	Patients with Sclerosis		Average Degree of Sclerosis†
		Num- ber	Per- cent- age			Num- ber	Per- cent- age	
No cause*.....	15	1	7	0.2+	15	12	80	1.3+
Pulmonary disease.....	6	3	50	0.7+	23	20	87	1.5+
Cardiac disease.....	2	1	..	2.0+	5	4	80	2.0+
Hypertension.....	3	1	..	0.3+	6	4	67	1.3+
Pulmonary and cardiac disease	3	1	..	0.3+	10	10	100	2.3+
Cardiac disease and hyperten- sion.....	3	2	67	1.0+
Pulmonary and cardiac disease and hypertension.....	3	3	100	2.3+
Pulmonary disease and hyper- tension.....	5	5	100	2.0+

* The patient with primary pulmonary vascular sclerosis is omitted from the "no cause" group of patients under 40.

† The average degree of sclerosis is obtained by adding together the pluses in each group and dividing by the number of cases in the group.

METHOD OF GRADING THE LESIONS

The thickness of the intima, either absolute or expressed as a percentage of the thickness of the vessel wall or of the vessel's external diameter, was the basis of classification. If in a given vessel there was a patch of sclerosis 0.2 mm. thick over one-fourth the circumference, the rest of the intima consisting of endothelium directly on the elastica interna, the "average thickness of the intima" for this vessel was taken as 0.2 divided by 4, or 0.05 mm. The "average intimal thickness" was obtained by adding the thickness of, for instance, twenty small muscular arteries and dividing by 20, to obtain the "average intimal thickness of the small muscular arteries." (Actually, for the small muscular arteries the intimal thickness was expressed as a percentage of the external diameter of the vessels, and it was these figures which were averaged, since obviously an intima 0.05 mm. thick is more important in a small than in a large artery.) The "average thickness of the intima of the small muscular arteries" for all the 16 cases in the "no cause" group in patients under 40 were then added together and divided by 16 to obtain the "average thickness of the intima" of the small muscular arteries in the "no cause"

group in patients under 40. Similarly, the average degree of the sclerosis in the small muscular arteries in the 16 cases in the "no cause" group in patients under 40 was obtained by adding together the plus signs given in each case for the degree of sclerosis of the small muscular arteries and dividing by 16. The same process was gone through for each type of vessel and for each of the etiologic subgroups. It must be stressed again that the resulting figures are useful only as a rough measure of the differences in the degree of sclerosis in the etiologic groups.

Stem of the Pulmonary Artery.—In children the intima consists of endothelium which lies directly on the elastica interna. In normal adults there may be an interposed layer of connective tissue up to 0.03 mm. thick. Sclerosis was considered to be present if the intima was more than 0.3 mm. thick. When it was from 0.03 to 0.1 mm. thick, the sclerosis was graded +; from 0.1 to 0.2 mm., ++, and from 0.2 to 0.3 mm., +++. By using these criteria it was found that sclerosis was present in 54 of the 96 cases in which the stem was examined (56 per cent). Table 6 shows the distribution and severity of the changes in the various age, sex and etiologic groups. In some cases the changes were patchy or diffuse or there was slight general thickening with patches of greater thickening (fig. 2). The greatest thickness in any case in the present series was 0.299 mm., or 33 per cent of the thickness of the media. The thickened intima usually consisted of dense connective tissue (occasionally looser and more fibrillar) which stained pink or sometimes a muddy brown or yellow with Van Gieson's stain. A few round and spindle cells were present in all cases. In 2 cases, some of the patches contained small groups of 3 or 4 lymphocytes, and in 1 case, the much thickened intima contained many round cells. In 1 case one of the sclerotic patches was edematous and contained many fibroblasts, lymphocytes and large mononuclears. Fat was present only occasionally and only in the thickest patches. A few fat spaces were present in the depths of the lesion in 1 case, and in 2 cases there were linear groups of foam cells. Elastic tissue was usually present in the patches and was absent in only 9 cases. In these the sclerosis was often marked and the connective tissue in the intimal plaques was loose, fibrillar and cellular. The internal elastic lamina frays out and disappears at the edges of such patches. Occasionally a large sclerotic patch was divided by a fine elastic fibril into a superficial portion which stained yellow and a deep portion which stained pink with Van Gieson's stain. In a few cases the elastica interna beneath the thickest patches was frayed into fine fibrils, either fragmented or missing.

In no case did the intima show an internal longitudinal musculo-elastic layer, but in 16 cases (all but 1 in patients over 40, and fairly evenly divided between the etiologic groups) the superficial 0.08 to 0.156 mm. of the media in places consisted of fine longitudinal elastic

TABLE 6.—*Relation of Histologic Changes in the Stem of the Pulmonary Artery to Age, Sex and Etiologic Factor*

Etiologic Factor	Age, Years	Males						Females													
		Patients with Sclerosis			Thickness of Intima, Mm.			Patients with Sclerosis			Thickness of Intima, Mm.										
		No. of Patients	Number	Percentage	Minimum	Maximum	Average	Average of Sclerosis	Minimum	Maximum	Average	Minimum	Maximum	Average of Sclerosis	Minimum	Maximum	Average				
No cause	0-39	7	3	43	0	0.050	0.016	0.6+	0.647	1.573	0.830	7	1	14	0	0.266	0.030	0.3+	0.531	0.929	0.727
	40-89	11	5	45	0	0.117	0.033	0.6+	0.780	1.463	1.012	4	2	50	0	0.070	0.022	0.5+	0.553	1.115	0.766
Pulmonary disease	0-39	5	4	80	0	0.299	0.061	1.2+	0.451	1.212	0.322	1	0	0	0.553
	40-89	10	7	70	0	0.098	0.033	0.7+	0.503	1.162	0.873	13	8	61	0	0.093	0.031	0.6+	0.531	1.323	0.870
Cardiac disease	0-39	1	0	0	..	1.262	..	1	1	0.233	..	3.0+	..	1.162	..
	40-89	4	2	50	0	0.051	0.026	0.5+	0.813	1.609	1.021	1	1	0.219	..	3.0+	..	0.707	..
Hypertension	0-39	1	1	..	0	0.059	..	1.0+	2	0	..	0	0.012	..	0	..	0.806	..
	40-89	2	1	..	0.020	0.030	0.030	0.5+	0.913	1.594	1.254	4	1	25	0.016	0.033	0.024	0.3+	0.780	1.139	0.955
Pulmonary and cardiac disease	0-39	3	1	33	0	0.249	0.083	1.0+	0.614	1.245	0.960
	40-89	8	7	88	0	0.266	0.037	1.4+	0.890	1.830	1.244	2	1	..	0.020	0.093	0.031	0.5+	..	0.850	..
Cardiac disease and hypertension	0-39
	40-89	2	2	..	0.043	0.133	0.113	1.5+	0.850	1.441	1.146	1	0	0.016	..	0	..	1.278	..
Pulmonary and cardiac disease and hypertension	0-39
	40-89	2	1	..	0.016	0.059	0.032	0.5+	0.946	1.162	1.054	1	0	0	..	0	..	0.631	..
Pulmonary disease and hypertension	0-39
	40-89	2	2	..	0.059	0.166	0.113	1.5+	..	1.196	..	3	3	..	0.039	0.247	0.108	1.7+	..	1.204	..

fibers with a few coarser circular fibers embedded in dense connective tissue containing few or no muscle cells. Sclerosis was never found to involve that layer, so it is impossible to confirm the results of those writers^p who have said that it begins there.

The only changes noted in the media were found to be as follows:

1. In aged patients there was often an increase in the connective tissue at the expense of the muscle and elastic tissue.
2. Beneath the large intimal plaques the media was often a little thinned.
3. There was a tendency to hypertrophy of the media in cases of heart failure in the "cardiac disease" group and in the "hypertension," "pulmonary and cardiac disease" and "pulmonary disease and hypertension" groups (table 6). Stains for fat were used in only a few cases, and the extension of fatty changes that have been said by some authors^q to occur was not observed. Laubry^r and others have said that in cases of pulmonary arteriosclerosis of whatever origin the medial elastic tissue is broken up and there is an increase in the amount of connective tissue. This description arouses the suspicion that the authors were not aware that in the normal pulmonary artery the elastic tissue is more broken up and the connective tissue more abundant than in the aorta.

The adventitia was usually normal, but in 5 cases there was a little focal or diffuse infiltration with lymphocytes, plasma cells and large mononuclears, and in 1 case the adventitia was edematous and infiltrated with lymphocytes, large mononuclears and a few polymorphonuclears. In 6 patients, all of whom were over 40, some of the vasa vasorum showed a thickened cellular intima.

Costa⁶³ said that in cases of pure mitral stenosis the intima is greatly thickened by dense connective tissue but no elastic tissue and little fat, while in cases of sclerosis due to other causes (even mitral stenosis if combined with regurgitation) there is a good deal of elastic tissue and fat. Others^s have not confirmed this finding. Ljungdahl¹⁷⁶ found the changes in his patients with pulmonary and cardiac diseases to be similar to those in his senile patients, except that in the patients with cardiac disease the changes were more marked, and fat was present only when the disease was severe and not, as in some senile patients, with only slight intimal thickening. The analysis of the cases in the present series shows that there was no essential difference in the histologic picture in the various etiologic groups, though the changes were on the whole least severe in the "no cause" group and though there was a

(p) 92, 114, 296.

(q) 114, 176.

(r) 160, 165.

(s) 92, 176, 296.

tendency toward thickening of the media in the cases of cardiac disease either alone or complicated by pulmonary disease or hypertension.

Large Elastic Arteries.—Arteries more than 1 mm. in external diameter, in which the media consists of elastic laminae with little muscle and connective tissue, are included in this category. The thickness of the intima relative to the thickness of the wall exclusive of the adventitia (the limits of which it was sometimes difficult to define) was used in grading the degree of sclerosis. This is less inaccurate than a comparison with the external diameter of the arteries, since the large arteries are usually collapsed and not circular in cross-section. Nevertheless, an attempt to determine the presence of medial hypertrophy was

TABLE 7.—*Distribution of Sclerosis of the Large Elastic Arteries, According to Age and Sex*

Age, Years	Males				Females			
	No. of Patients	Patients with Sclerosis		Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis		Average Degree of Sclerosis
		Num- ber	Percent- age			Num- ber	Percent- age	
0-9	1	0	..	0	3	1	..	0.3+
10-19	9	7	78	1.6+
20-29	3	3	..	1.3+	2	2	..	2.0+
30-39	4	4	..	2.0+	6	5	83	1.6+
40-49	10	10	100	1.8+	3	3	..	2.0+
50-59	14	14	100	2.0+	9	9	100	1.9+
60-69	12	11	91	1.9+	8	8	100	1.9+
70-79	4	4	..	2.0+	7	7	100	1.6+
80-89	2	2	..	2.0+
Totals*	57	53	93	1.7+	40	37	93	1.7+

* Of the total number of 97 patients, 90 (93 per cent) showed sclerosis of the large elastic arteries (average degree of sclerosis, 1.7+). Of the 28 patients less than 40 years of age, 22 (78 per cent) showed sclerosis (average degree, 1.3+). Of the 69 patients over 40 years of age, 68 (98 per cent) showed sclerosis (average degree, 1.9+).

made by expressing the thickness of the media as a percentage of the external diameter of the vessel, the mean of the greatest and smallest diameters being taken for this purpose. The measurements of many large arteries in each case were averaged, as explained previously, in determining the average intimal and medial thickness in each case and in each group. The presence of any connective tissue between the endothelium and the elastica interna was interpreted as indicating the presence of sclerosis. If the average thickness of the intima was less than 20 per cent of that of the wall of the vessel, the sclerosis was graded + (individual sclerotic patches were as much as 40 per cent of the total thickness of the wall); from 20 to 30 per cent, ++; from 30 to 40 per cent, + + +, and over 40 per cent, + + + +.

Table 7 shows the age and sex distribution of the sclerotic changes. Sclerosis was present in 22 of 28 patients under 40 (78 per cent) and

in 68 of 69 over 40 (98 per cent). Thus sclerosis is common in youth and is almost constant and often severe in and after middle age.

Table 8 shows the incidence and severity of sclerosis in the various etiologic groups. In the "no cause" group, of the 16 patients under 40, 5 showed no sclerosis and 4 of these were under 20. In 4 of the remaining 11 patients there was only an occasional small patch of sclerosis in a few arteries. In 7 cases the sclerosis was more marked. The thickness of the media and the diameter of the lumen were normal. This table shows that in patients over 40 sclerosis was common even in

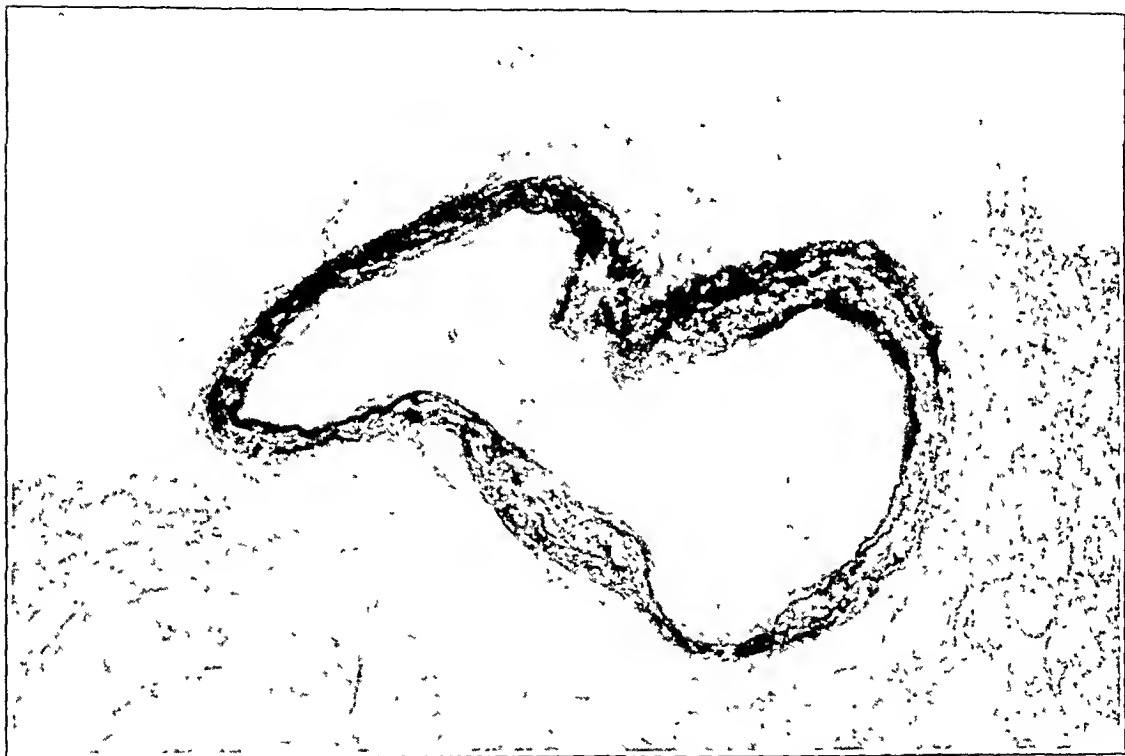


Fig. 5.—Photomicrograph showing a moderate degree of arteriosclerosis of a large elastic artery ($\times 17$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). The media is thinned beneath the thickest portion of the sclerotic patch.

the absence of factors which are usually thought to raise the pulmonary arterial pressure (14 of 15 patients, or 93 per cent). The presence of such factors was associated with an increase in the frequency of sclerosis in patients under 40 and possibly with a slight increase in the severity of the lesions in patients over 40.

The changes resembled those in the stem and showed no essential differences in the various etiologic groups. There was slight or marked intimal thickening (fig. 5), involving part or all the circumference of few or many arteries. The intimal connective tissue was usually dense

TABLE 8.—Distribution of Sclerosis in Large Elastic Arteries According to Age, Sex and Etiologic Factor				
	Patients with Sclerosis.	Males	Females	Thickness of Intima.
Age				
Sex				
Etiologic Factor				

Etiologic Factor		Males												Females																					
		Patients with Sclerosis				Thickness of Intima*				Thickness of Media†				Diameter of Lumen†				Patients with Sclerosis				Thickness of Intima*				Thickness of Media†				Diameter of Lumen†					
		No. of Patients		Percentage		Minimum		Maximum		Average		Minimum		Maximum		Average		Minimum		Maximum		Average		Minimum		Maximum		Average		Minimum		Maximum		Average	
		No. of Patients	Percentage	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average		
No cause	0-39	9	7	0	23	36	16	6	5	15	8	60	89	87	1.4+	7	4	57	0	37	12	5	13	9	67	90	76	1.0+	1.0+	1.0+	76	80	1.9+		
	40-89	10	9	0	23	36	16	6	5	15	8	60	89	87	1.4+	5	3	100	10	25	17	5	11	8	68	87	80	1.0+	1.0+	1.0+	80	81	1.9+		
Pulmonary disease	0-39	5	5	100	9	23	14	7	17	11	60	83	73	1.4+	1	1	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+			
	40-89	10	10	100	5	38	16	2	13	7	67	90	81	1.4+	13	13	100	10	25	17	5	11	8	68	87	80	1.0+	1.0+	1.0+	80	81	1.9+			
Cardiac disease	0-39	1	1	100	30	26	12	4	14	10	70	90	77	1.3+	1	1	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+			
	40-89	4	4	100	8	26	12	4	14	10	70	90	77	1.3+	13	13	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+			
Hypertension	0-39	2	2	100	23	18	10	10	10	70	90	77	1.3+	1	1	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+				
	40-89	2	2	100	23	18	10	10	10	70	90	77	1.3+	1	1	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+				
Pulmonary and cardiac disease	0-39	3	3	100	23	18	10	10	10	70	90	77	1.3+	1	1	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+				
	40-89	9	9	100	14	42	31	6	15	10	34	87	63	2.8+	4	4	100	9	13	11	6	12	10	75	89	87	1.0+	1.0+	1.0+	87	81	2.0+			
Cardiac disease and hypertension	0-39	2	2	100	23	18	10	10	10	70	90	77	1.3+	1	1	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+				
	40-89	2	2	100	23	18	10	10	10	70	90	77	1.3+	1	1	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+				
Pulmonary and cardiac disease and hypertension	0-39	2	2	100	23	18	10	10	10	70	90	77	1.3+	1	1	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+				
	40-89	2	2	100	23	18	10	10	10	70	90	77	1.3+	1	1	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+				
Pulmonary disease and hypertension	0-39	2	2	100	23	18	10	10	10	70	90	77	1.3+	1	1	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+				
	40-89	2	2	100	23	18	10	10	10	70	90	77	1.3+	1	1	100	5	45	12	5	15	10	47	96	73	1.0+	1.0+	1.0+	73	75	1.9+				

* The thickness of the intima is expressed as a percentage of the wall of the vessel exclusive of the adventitia.

† The thickness of the media and the diameter of the lumen are expressed as percentages of the external diameter of the vessel.

*

7

and hyaline, but in 10 cases some of the patches consisted of loose fibrillar connective tissue. This change occasionally was confined to part of a sclerotic patch. Usually the connective tissue contained a few round and spindle cells. In 6 cases some of the thickest patches contained small groups of lymphocytes. In 1 case there were numbers of large round cells. In 13 cases some of the patches showed foci of lymphocytes, large mononuclears and an occasional polymorphonuclear, and in 1 case these were so dense as to suggest inflammatory infiltration. In 2 cases in which there was acute arteritis due to the presence of septic emboli, there were many polymorphonuclears in the intimal patches. Red blood cells, enmeshed in a delicate reticulum, were present in a few patches in 1 case. The intimal plaques were infiltrated with tumor cells in 1 case of mediastinal tumor. Smooth muscle cells, chiefly longitudinal, were present in the thickest intimal patches in 8 cases. These cells were sometimes numerous but were usually scattered and did not form a definite compact layer in the thickened intima. Fat was present within groups of large foam cells in 29 cases. The foam cells were often arranged in rows and usually were present only in the thickest patches, though in some arteries in one case a single row of foam cells, embedded in a minimal amount of connective tissue, alone separated the endothelium from the elastica interna. In 7 cases spaces from which fat had been dissolved were present in the thickened intima. Fat seemed to be present in the intimal plaques rather more commonly in cases of pulmonary disease, either alone or combined with heart disease, than in the other groups.

In 1 case in which the lumen contained an organizing thrombus, capillaries were present in the thickened intima.

In 13 cases there was no elastic tissue except the elastica interna in the sclerotic patches. In most cases there were few or many fine, rather poorly staining elastic fibrils in the depths of the patches. Usually these were irregularly arranged, but in 15 cases in some of the patches the fibrils ran parallel to, and seemed to be split off from, the elastica interna. In 2 cases in some patches the elastica interna split to enclose a wide oval of connective tissue full of fine elastic fibrils. In 8 cases some of the thickest sclerotic patches were subdivided by a fine elastic fibril (in 1 case by a narrow sheaf of fine fibrils) into a superficial portion which stained yellow and a deep portion which stained pink with Van Gieson's stain. The elastica interna was usually a coarse, densely staining band continuous around the whole circumference of the vessel, but in 18 cases in some of the patches it either frayed out into fibrils or became fragmented, and beneath some of the thicker patches it disappeared altogether. In 1 case the medial elastic laminae beneath a thick patch also disappeared.

These intimal changes in themselves rarely caused marked narrowing of the lumen, though in some cases the lumen was narrowed or obliterated by thrombi.

The media was often thinned beneath the thickest patches. The average thickness of the media was 8 per cent of the external diameter of the vessel excluding the adventitia, in the cases of the "no cause" group patients over 40 and in the cases of the "cardiac disease" group patients under 40. This is less than the normal average (9.8 per cent), though within the normal range. In both cases in the latter group congestive heart failure was present, so that there is no evidence that congestive failure (presumably associated with a high pulmonary arterial pressure) causes medial hypertrophy in the large elastic arteries. There was no tendency for the media to be thickened except possibly in the "pulmonary disease and hypertension" group, and there the numbers were too small for statistical accuracy. In 1 case some longitudinally arranged muscle was present in patches. In 3 patients over 40 there was rather more connective tissue than usual in the outer part of the media. In 1 patient under 40 in the "pulmonary disease" group the superficial 0.06 mm. of the media of one artery in a long stretch consisted of dense connective tissue with no muscle or elastic tissue. In 1 patient under 40 in the "hypertension" group one artery in the superficial half of its media showed no elastic laminae but only irregular elastic fibrils, a great deal of connective tissue and little muscle, chiefly longitudinally arranged.

In the cases reported in the literature, also, there were no distinctive variations in the histologic appearances of the sclerosis according to the etiologic factor present, and the changes reported were similar to those just described, though usually no detailed description was given.^t In many cases changes were also described in the media,^u the commonest being the extension of fatty degeneration, sometimes with a little calcification, into its superficial part. This was never observed in the present series. An excess of fibrous tissue was noted in the media more commonly than in the present series. In some cases there was a proliferation of the medial elastic tissue, sometimes resulting in thickening of the media.³⁰⁸ Wiesel^v described focal edema of the media, followed by fibrosis and sometimes calcification, as a sequel of acute infections. In the present series the medial changes were much less conspicuous than they seemed to be in the cases reported in the literature.

(*t*) 64, 78, 94, 102, 114, 136, 150, 160, 161, 165, 174, 176, 186, 193, 250, 276, 284, 295, 296, 306, 331.

(*u*) 64, 94, 102, 136, 160, 161, 165, 174, 176, 250, 284, 295, 307, 308, 324, 325.

(*v*) 324, 325.

The adventitia only occasionally showed abnormalities in the present series. In 2 cases of acute septic arteritis due to the presence of septic emboli in the lumen the adventitia was infiltrated with polymorphonuclears. In 2 cases (in 1 of which the lumen contained a thrombus) there was focal round cell infiltration of the adventitia. In 1 case opposite a parietal thrombus in the lumen the adventitia showed dilated capillaries, endarteritis obliterans of the vasa vasorum and a great deal of infiltration with lymphocytes and large mononuclears. The vasa vasorum showed a thick cellular intima in 3 cases, all in patients over 40. It was invaded by tumor cells in 1 case of mediastinal tumor and by caseous tuberculosis in another case.

TABLE 9.—*Distribution of Sclerosis in Small Muscular Arteries According to Age and Sex*

Age, Years	Males				Females			
	No. of Patients	Patients with Sclerosis		Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis		Average Degree of Sclerosis
		Num- ber	Pereent- age			Num- ber	Pereent- age	
0-9	2	1	..	1.0+	3	1	..	0.7+
10-19	9	6	67	1.2+
20-29	3	3	..	2.3+	2	1	..	1.0+
30-39	5	4	80	1.0+	6	6	100	1.7+
40-49	10	10	100	1.8+	3	3	..	2.3+
50-59	14	13	93	2.0+	9	8	89	1.6+
60-69	12	12	100	2.5+	8	8	100	2.5+
70-79	4	4	..	1.8+	8	8	100	2.8+
80-89	2	2	..	2.5+
Totals*	59	53	90	1.7+	41	37	90	2.0+

* Of the 100 patients, 90 (90 per cent) showed sclerosis of the small muscular arteries (average degree, 1.8+). Of the 30 patients less than 40 years of age 23 (73 per cent) showed sclerosis (average degree, 1.3+). Of the 70 patients over 40 years of age, 65 (97 per cent) showed sclerosis (average degree, 2.2+).

Small Muscular Arteries.—Less attention has been paid in the literature to the small muscular arteries, and it is frequently difficult to be sure that the muscular arteries are meant when the authors speak of “small arteries,” since the accompanying illustrations often show arteries of the elastic type. Tables 9 and 10 show the distribution of sclerosis of the muscular arteries in the present series according to age, sex and etiologic factors. Normally the intima consists of endothelium directly on the elastica interna, and sclerosis was considered to be present if any connective tissue intervened. When the average thickness of the intima was less than 2 per cent of the external diameter of the vessel excluding the adventitia the sclerosis was graded +, when the intimal thickness was from 2 to 10 per cent of the diameter, ++; when it was from 10 to 20 per cent, +++ and when it was over 20 per cent, ++++. Sclerosis of the muscular arteries was present in 90 per cent of cases and was evenly distributed between the sexes, though slightly more

TABLE 10.—*Distribution of Sclerosis of Small Muscular Arteries According to Age, Sex and Etiologic Factor **

Etiologic Factor	Age, Years	Males						Females					
		Patients with Sclerosis			Patients with Sclerosis			Patients with Sclerosis			Patients with Sclerosis		
		No. of Patients	Per-centage	Thickness of Intima	Thickness of Media	Diameter of Lumen	Average Degree of Sclerosis	No. of Patients	Per-centage	Thickness of Intima	Thickness of Media	Diameter of Lumen	Average Degree of Sclerosis
No cause	0-39	9	55	1 (0-2)	10 (4-18)	79 (65-87)	0.7+	7	4	2 (0-8)	9 (6-13)	77 (68-86)	0.7+
	40-89	10	100	8 (1-17)	10 (8-16)	64 (42-86)	1.5+	5	4	2 (0-4)	9 (6-13)	75 (56-89)	1.2+
Pulmonary disease	0-39	5	100	7 (1-16)	13 (8-20)	64 (58-78)	1.8+	1	1	6	14	58	2.0+
	40-89	10	100	7 (1-14)	10 (6-15)	68 (51-80)	2.1+	13	100	11 (1-17)	11 (7-17)	54 (22-77)	2.4+
Cardiac disease	0-39	1	1	7	12	66	2.0+	1	1	6	11	67	2.0+
	40-89	4	100	6 (1-9)	9 (7-11)	72 (61-79)	1.8+	1	1	2	8	79	1.0+
Hypertension	0-39	1	0	0	9	82	0	2	2	8 (5-10)	13 (10-16)	58 (57-60)	2.0+
	40-89	2	2	7 (6-8)	9 (8-9)	68 (60-75)	2.0+	4	100	8 (2-12)	10 (9-11)	62 (55-69)	2.0+
Pulmonary and cardiac disease	0-39	3	2	4 (1-7)	13 (12-13)	73 (71-75)	1.7+	2	2	12 (12-12)	13 (11-19)	49 (47-53)	3.0+
	40-89	8	89	7 (0-11)	11 (8-15)	56 (39-76)	2.2+	2	2	12 (12-12)	13 (11-19)	49 (47-53)	3.0+
Cardiac disease and hypertension	0-39	2	2	4 (2-7)	9 (7-10)	78 (73-83)	1.5+	1	1	7	4	77	2.0+
	40-89	2	2	6 (2-10)	9 (7-11)	72 (62-82)	2.0+	1	1	2	7	82	1.0+
Pulmonary disease and hypertension	0-39	2	2	12 (10-14)	16 (13-19)	56 (53-59)	3.0+	3	3	12 (11-12)	9 (7-10)	60 (57-62)	3.0+
	40-89	2	2	12 (10-14)	16 (13-19)	56 (53-59)	3.0+	3	3	12 (11-12)	9 (7-10)	60 (57-62)	3.0+

* All measurements are expressed as percentages of the external diameter of the vessel exclusive of the adventitia. The first figure in the column represents the average percentage and the figures in the parentheses represent the extremes.

severe in the females. It was present in 22 of 30 patients under 40 (73 per cent) and was practically constant in those over 40 (68 of 70, or 97 per cent). It was also more severe in patients over 40. Table 10 shows the incidence and severity of the sclerosis in the various etiologic groups. Sclerosis is least frequent and least severe in the "no cause" group in patients under 40. Only 9 of the 16 patients showed sclerosis, and with the exception of the case of primary sclerosis and 1 other case in which it was marked, the sclerosis was slight and patchy and involved only a few arteries in each case. Slight sclerosis of the small pulmonary arteries is thus not uncommonly present in young persons in whom there is no evidence of a raised pulmonary arterial pressure during life, a point which appears not to have been previously appreciated. Of the 15 patients over 40 in the "no cause" group 14, or 93 per cent, showed sclerosis, though in all but 1 patient some arteries were normal and in 7 patients there was only slight patchy sclerosis of a few arteries. In 6 patients the lumen of many arteries was narrowed by the intimal thickening. Thus, even in the absence of factors thought to raise the pulmonary arterial pressure, sclerosis of the small muscular arteries is almost constant in patients over 40 and may sometimes be marked. Ljungdahl,¹⁷⁶ who is the only author who has described systematic examination of the small arteries in elderly persons in the absence of factors likely to raise the pulmonary arterial pressure, stated that sclerosis is common though less marked than in the larger arteries.

In the "pulmonary disease" group all the patients under 40 showed sclerosis, though in 3 only a few arteries showed a few small patches. In the remaining patients many arteries showed marked patchy or diffuse intimal thickening, often with narrowing of the lumen. The 23 patients over 40 showed sclerosis, though in 4 only a few arteries showed small patches. In 13 patients practically every artery showed intimal thickening, sometimes with narrowing of the lumen. In the remaining 6 patients there was an intermediate degree of sclerosis.

In the "cardiac disease" group both patients under 40 showed moderate sclerosis affecting many but not all the vessels. All the patients over 40 showed slight to moderate sclerosis. In all cases most of the small arteries were normal, but in 1 case the lumen of some vessels was narrowed by intimal thickening.

In the "hypertension" group sclerosis was present in 2 of the 3 patients under 40, in both of whom many arteries were normal. In all the patients over 40 sclerosis was present. Many arteries were normal and some had lumens narrowed by marked intimal thickening.

All the patients in the "pulmonary and cardiac disease" group showed moderate to marked sclerosis. In 3 the lumen of most vessels was much narrowed by intimal thickening. In the "cardiac disease and hypertension" and "pulmonary and cardiac disease and hypertension"

groups all the patients showed slight to moderate sclerosis. In the "pulmonary disease and hypertension" group all the patients showed marked sclerosis with narrowing of the lumen.

Thus, the observations indicate that sclerosis of the small muscular arteries is almost constant (though sometimes in only a few vessels) in patients over 40, irrespective of the presence or absence of chronic pulmonary or cardiac disease, but that the frequency of sclerosis in those under 40 and its severity in those over 40 are somewhat greater

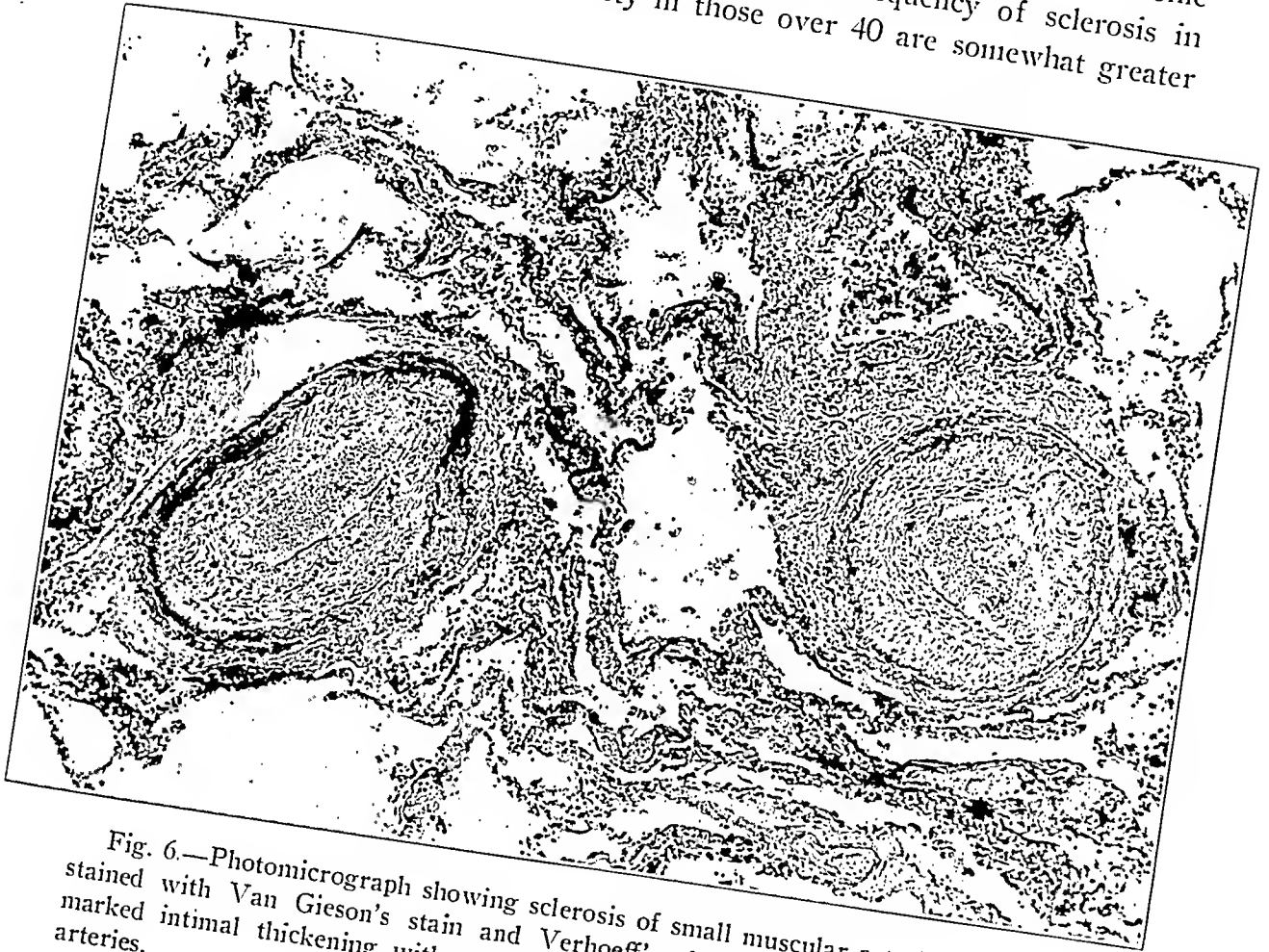


Fig. 6.—Photomicrograph showing sclerosis of small muscular arteries ($\times 192$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). There is marked intimal thickening with narrowing of the lumen in two small muscular arteries.

in the presence of chronic cardiac or pulmonary disease, separately or together.

The histologic changes (fig. 6) were in most respects similar to those in the large arteries and show no constant differences in the various groups. Normally the intima consists of endothelium directly on the elastica interna. The presence of any intervening connective tissue was taken to indicate the presence of sclerosis. The intimal thickening was at times slight and patchy, involving only a small portion of the circumference of the vessel, and at times there was marked thickening of

the intima all around the circumference of the vessel with marked narrowing of the lumen. The connective tissue was usually dense; it stained pink or yellowish with Van Gieson's stain and contained a few round or oval cells. In 4 cases the connective tissue of some of the patches was loose, fibrillar and cellular. In 1 case the intima of some of the larger muscular arteries showed foci of lymphocytes, large mononuclears and a few polymorphonuclears. In 1 case in which there was a chronic pulmonary abscess some of the vessels near the abscess showed dense infiltration of the intima with lymphocytes and large mononuclears. Polymorphonuclears were present in the thickened intima of one artery the lumen of which contained a septic embolus. In two cases the thickened intima was infiltrated with tumor cells. Fat was less common than in the large arteries, as is the case with sclerosis of the systemic vessels,²⁶ but it was present in foam cells in 2 cases and free in the thickened intima in 3 cases, in each case only in the larger of the muscular arteries. Elastic tissue was less abundant than in the large elastic arteries. There was a little poorly staining elastic tissue in some of the sclerotic patches in 20 cases, and in 7 cases it ran parallel to, and appeared to be split from, the elastica interna. In 1 case some of the thickest sclerotic patches were divided by a single elastic fibril into a superficial layer which stained yellowish and a deep layer which stained pink with Van Gieson's stain. In many cases the elastica interna was fragmented or missing beneath some of the thickest patches.

The media was often somewhat thinned beneath the thickest sclerotic patches. It showed in many cases other changes (fibrosis, inflammatory round cell infiltration and invasion by neoplasm and tuberculosis), to be described in the appropriate sections. The adventitia also showed similar changes.

Thus, the character of the changes was on the whole similar to that in the larger vessels and to that in small systemic muscular arteries and did not differ with the etiologic factor.

Arterioles and Venules.—These can be distinguished only if seen joining an artery or vein. Normally they consist of endothelial tubes, around which single, or occasionally double, elastic fibers are wound spirally. The presence of any connective tissue between the endothelium and the elastic fiber is abnormal. If the thickness of the vessel wall was less than 10 per cent of the external diameter, the sclerosis was graded +; if from 10 to 15 per cent, ++; if from 15 to 25 per cent, + + +, and if over 25 per cent, + + + +. Table 11 shows that sclerosis was present in 93 of 99 cases (94 per cent) and was equally common in males and females. It was present in 25 of 30 patients (83 per cent) under 40 and in 68 of 69 patients (98 per cent) over 40. Four of the 6 patients without sclerosis were children under

10 years of age. Table 12 shows that sclerosis of the arterioles and venules was almost constant in patients over 40 even in the absence of factors thought to raise the pulmonary arterial pressure, and it was common even in patients under 40. When cardiac or pulmonary disease or hypertension or any combination of these was present, the frequency and severity of sclerosis in patients under 40 were increased, but there was no significant increase either in the frequency or in the severity of sclerosis in patients over 40.

The sclerosis, when present, usually was more widespread than in the case of the larger vessels and involved most or all the arterioles and venules. Occasionally the change was patchy, but usually the whole

TABLE 11.—*Distribution of Sclerosis of the Arterioles and Venules According to Age and Sex*

Age, Years	Males				Females			
	No. of Patients	Patients with Sclerosis		Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis		Average Degree of Sclerosis
		Num- ber	Percent- age			Num- ber	Percent- age	
0-9	2	1	..	1.5+	3	0	..	0
10-19	9	8	89	1.4+
20-29	3	3	..	3.7+	2	2	..	2.0+
30-39	5	5	100	2.0+	6	6	100	2.0+
40-49	10	10	100	2.0+	3	3	..	2.0+
50-59	14	13	93	2.0+	8	8	100	2.0+
60-69	12	12	100	2.7+	8	8	100	2.8+
70-79	4	4	..	2.5+	8	8	100	2.6+
80-89	2	2	..	2.5+
Totals*	59	56	95	2.1+	40	37	93	2.2+

* Of the 99 patients 93 (94 per cent) showed sclerosis of the arterioles and venules (average degree, 2.1+). Of the 30 patients less than 40 years of age 25 (83 per cent) showed sclerosis (average degree, 1.8+). Of the 69 patients over 40 years of age 68 (98 per cent) showed sclerosis (average degree, 2.3+).

circumference of the vessel was involved (fig. 7). Between the endothelium and the elastic fiber there was a layer of connective tissue, usually dense and almost acellular, which stains pink or occasionally brownish or yellowish with Van Gieson's stain. In 2 cases the vessels near a chronic pulmonary abscess and a patch of fibrocaseous tuberculosis, respectively, showed thickening of their walls by looser connective tissue which contained many lymphocytes and fibroblasts. In several cases a few round cells lay in lacunae hollowed out between the connective tissue and the elastic fiber. In 2 cases the thickened wall of the vessel was infiltrated with tumor cells. The endothelium of many vessels was swollen in 2 cases and it was proliferated in a case of primary sclerosis in a boy of 11 in a few vessels, where the change had spread from the small muscular arteries, and in 1 other case near pyemic abscesses of the lung.

TABLE 12.—*Distribution of Sclerosis of the Arterioles and Venules According to Age, Sex and Etiologic Factor**

Etiologic Factor	Age, Years	Males						Females					
		No. of Patients	Patients with Sclerosis		Thickness of Wall of Vessel	Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis		Thickness of Wall of Vessel	Average Degree of Sclerosis		
			Number	Percentage				Number	Percentage				
No cause	0-39	9	7	78	7 (2-15)	0.9+	7	5	72	11 (3-24)	1.2+		
	40-59	10	10	100	17 (8-29)	2.3+	5	5	100	14 (8-19)	2.0+		
Pulmonary disease	0-39	5	5	100	22 (4-32)	3.4+	1	0	..	6	0		
	40-59	10	10	100	15 (5-26)	2.2+	13	13	100	17 (7-34)	2.5+		
Cardiac disease	0-39	1	1	..	24	3.0+	1	1	..	21	3.0+		
	40-59	4	4	..	13 (8-16)	1.5+	1	1	..	15	2.0+		
Hypertension	0-39	1	1	..	15	2.0+	2	2	..	16 (11-17)	2.5+		
	40-59	2	2	..	14 (10-17)	2.5+	1	1	..	19 (12-27)	3.0+		
Pulmonary and cardiac disease	0-39	3	3	..	21 (18-24)	3.0+		
	40-59	8	7	88	17 (5-28)	2.3+	2	2	..	11 (10-12)	2.0+		
Cardiac disease and hypertension	0-39		
	40-59	2	2	..	15 (10-19)	2.0+	1	1	..	22	3.0+		
Pulmonary and cardiac disease and hypertension	0-39		
	40-59	2	2	..	13 (11-15)	2.0+	1	1	..	17	3.0+		
Pulmonary disease and hypertension	0-39		
	40-59	2	2	..	14 (10-18)	2.0+	3	3	..	21 (15-26)	3.0+		

* The thickness of the wall of the vessel is expressed as a percentage of the total external diameter of the vessel. When measurements are given, the first figure represents the average and the figures in parentheses represent the extremes.

Though the changes were usually widely and evenly spread throughout the lungs, in 1 case of fibrocaceous tuberculosis and in 1 case in which there were secondary deposits of growth in the lungs, the vessels near the lesions were greatly thickened, while those elsewhere were mostly normal.

Capillaries.—The capillaries showed no important changes except dilatation and engorgement in cases of congestive heart failure. These changes are of great importance in the production of the symptoms of

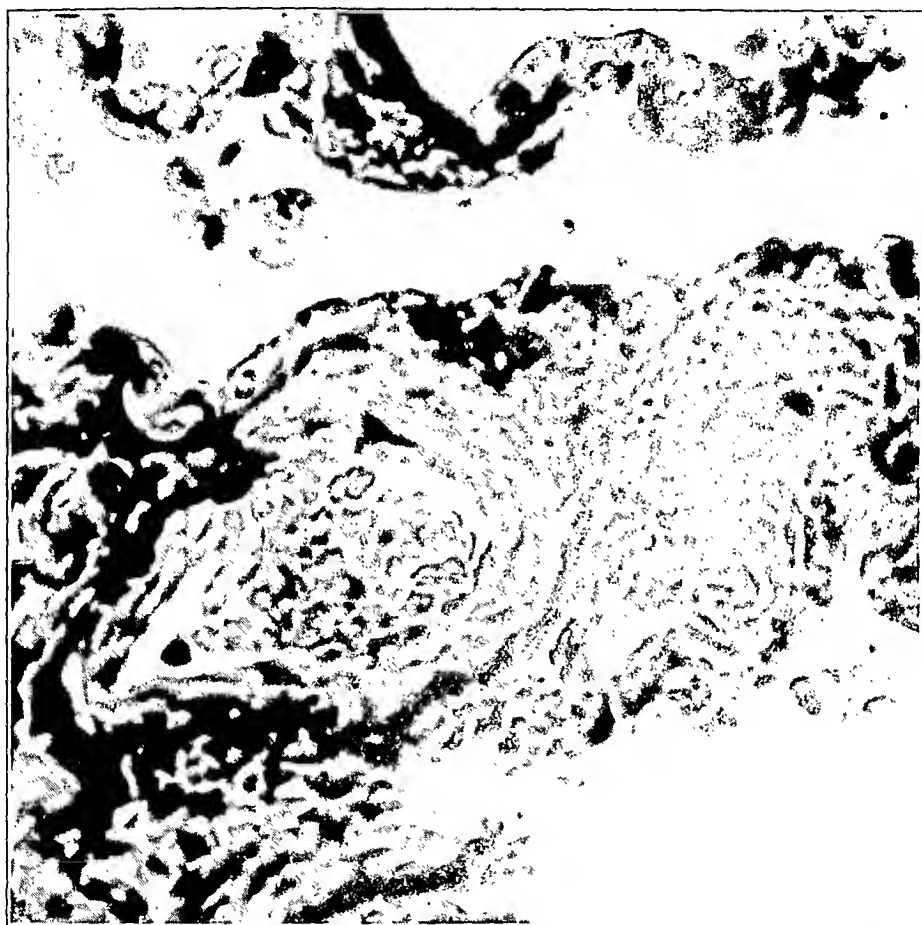


Fig. 7.—Photomicrograph showing sclerosis of an arteriole or venule ($\times 675$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). There is fairly marked thickening of the connective tissue within a single elastic fiber. The lumen is narrowed.

heart failure. Moschowitz²⁶ regarded them as part of an "arterio-capillary fibrosis" similar to that described in the systemic circulation by Gull and Sutton.

Small Veins.—Little attention has been paid in the literature to sclerosis of the pulmonary veins. Benda²⁷ observed only 1 case of sclerosis of the pulmonary veins, that of a woman of 28 with chronic

(w) 212, 213, 214.

nephritis and nephrosis; the main pulmonary veins showed intimal thickening with deposition of fat. Moschowitz²¹³ said that in cases of mitral stenosis sclerosis of the pulmonary veins is almost as common as sclerosis of the arteries. Prevot²⁴² observed no gross changes in the pulmonary veins in 60 cases but marked microscopic changes in 8 and moderate changes in 30. The changes were usually not so severe as in the arteries. There were fatty degeneration of the elastica interna and of the medial elastic tissue and thickening of the intima, with much deposition of fat either in foam cells or free in the connective tissue. The elastica interna often split as it approached the sclerotic patch. Brüning⁴⁸ frequently noted sclerosis of the pulmonary veins in his patients, though it was not so common or severe as in the arteries. It was most marked in patients with congestive heart failure, but was not confined to them. Zinsser³³⁵ noted patchy intimal thickening with fatty change in only 1 of 9 cases of mitral stenosis. Ljungdahl¹⁷⁶ found gross changes in 17 of 36 cases of cardiac disease. Microscopic changes in the small veins were much slighter and less common. There were no changes in any of 45 patients with chronic pulmonary disease. In this he agreed with Moschowitz.²¹³ Rosenthal²⁵⁶ observed circumscribed intimal thickening in many small veins in 2 of his 3 patients with pulmonary vascular sclerosis and pneumoconiosis. Thus, in the few cases in which sclerosis of the pulmonary veins has been described, it was found chiefly in the large veins and was less common and slighter in the small veins.

Veins less than 1 mm. in external diameter are considered in this section. Up to a diameter of 0.25 mm. the veins have the same structure as the venules and consist of an endothelial tube around which a single elastic fiber is wound. When the diameter is over 0.25 mm., there are two or more elastic fibers with a little connective tissue and an occasional muscle cell. The normal thickness of the wall is from 2 to 7 per cent of the external diameter (average, 4 per cent). The occurrence of any connective tissue between the endothelium and the elasticofibromuscular layer representing the media was considered as evidence of sclerosis. When the average thickness of the wall of the vein was less than 10 per cent of the external diameter the sclerosis was graded +; between 10 and 15 per cent, ++; between 15 and 25 per cent, +++, and over 25 per cent, +++++.

Table 13 shows that sclerosis of the small veins was present in 90 of 99 patients (91 per cent) and was evenly distributed between the sexes. It was present in 22 of 29 patients under 40 (76 per cent) and in 68 of 70 patients over 40 (97 per cent). Table 14 shows that even in the absence of factors thought to raise the pulmonary arterial pressure, sclerosis of the small veins was constant in patients over 40. The presence of cardiac or pulmonary disease, alone or together, was asso-

ciated with an increase in the incidence of sclerosis in patients under 40 and with an increase in its severity in patients over 40. That the frequency and severity of sclerosis of the small pulmonary veins were increased in cases of pulmonary disease (contrary to the findings of Moschowitz and Ljungdahl) is noteworthy, since any obstruction to the pulmonary circulation is in the capillaries and the pressure in the veins might be expected to be low rather than high.

The changes consisted in the appearance of a layer of connective tissue between the endothelium and the medial elastic tissue. This was sometimes all around the circumference and sometimes present only in patches. In the affected patients most of the small veins (less than 0.25 mm. in diameter) are involved, while the larger veins, with a more

TABLE 13.—*Distribution of Sclerosis of Small Veins According to Age and Sex*

Age, Years	Males				Females			
	Patients with Sclerosis				Patients with Sclerosis			
	No. of Patients	Num- ber	Percent- age	Average Degree of Sclerosis	No. of Patients	Num- ber	Percent- age	Average Degree of Sclerosis
0-9	2	1	..	1.0+	3	0	..	0
10-19	9	7	78	1.7+
20-29	3	3	..	2.3+	1	1	..	4.0+
30-39	5	5	100	1.2+	6	5	83	1.7+
40-49	10	9	90	1.8+	3	3	..	2.3+
50-59	14	13	93	1.7+	9	9	100	2.2+
60-69	12	12	100	2.2+	8	8	100	2.4+
70-79	4	4	..	2.5+	8	8	100	2.3+
80-89	2	2	..	2.5+
Totals*	59	54	92	1.8+	40	36	90	1.9+

* Of the total number of 99 patients, 90 (91 per cent) showed sclerosis of the small veins (average degree, 1.9+). Of the 29 patients less than 40 years of age, 22 (76 per cent) showed sclerosis (average degree, 1.6+). Of the 70 patients over 40 years of age, 68 (97 per cent) showed sclerosis (average degree, 2.1+).

definite media, show less severe changes and sometimes many of them are normal. This was so in the cases in the "pulmonary disease" group, though in only 2 of the 23 patients over 40 were the larger veins entirely normal. In some cases the thickening of the intima was great enough to cause narrowing of the lumen, and in 1 case of healed pulmonary tuberculosis many of the small veins in the scarred areas were completely obliterated by an overgrowth of connective tissue. In 4 other cases in patients with fibrocaceous tuberculosis or chronic pulmonary abscess the changes in the veins were practically confined to the neighborhood of the pulmonary lesions.

The thickened intima usually consisted of dense, almost hyaline connective tissue which stained pink or occasionally yellowish or brownish with Van Gieson's stain and which was almost acellular. In 9 cases the veins that were near chronic or acute pulmonary abscesses

TABLE 14.—*Distribution of Sclerosis of Small Veins According to Age, Sex and Etiologic Factor**

Etiologic Factor	Age, Years	Males					Females				
		No. of Patients	Patients with Sclerosis		Thickness of Wall of Vessel	Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis		Thickness of Wall of Vessel	Average Degree of Sclerosis
			Number	Percentage				Number	Percentage		
No cause	0-39	9	6	67	7 (2-10)	0.7+	6	4	67	8 (3-20)	1.0+
	40-89	10	10	100	12 (4-19)	1.5+	5	5	100	14 (6-23)	1.8+
Pulmonary disease	0-39	5	5	100	22 (10-28)	2.8+	1	0	..	7	0
	40-89	10	10	100	15 (7-25)	2.0+	13	13	100	22 (8-36)	2.5+
Cardiac disease	0-39	1	1	..	26	4.0+	1	1	..	28	4.0+
	40-89	4	3	..	10 (3-20)	1.2+	1	1	..	29	4.0+
Hypertension	0-39	1	1	..	8	1.0+	2	1	..	21 (6-36)	2.0+
	40-89	2	2	..	12 (8-15)	1.5+	4	4	..	12 (11-14)	2.0+
Pulmonary and cardiac disease	0-39	3	3	..	18 (10-25)	2.0+
	40-89	8	7	88	17 (3-29)	2.0+	2	2	..	21 (13-29)	3.0+
Cardiac disease and hypertension	0-39
	40-89	2	2	..	16 (7-25)	2.0+	1	1	..	15	2.0+
Pulmonary and cardiac disease and hypertension	0-39
	40-89	2	2	..	25 (15-35)	3.0+	1	1	..	8	1.0+
Pulmonary disease and hypertension	0-39
	40-89	2	2	..	30 (21-40)	3.5+	3	3	..	16 (11-18)	2.3+

* The thickness of the wall of the vessel is expressed as a percentage of the total external diameter. Where measurements are given, the first figure represents the average and the figures in parentheses represent the extremes.

or patches of active pulmonary tuberculosis were narrowed by a thick layer of loose connective tissue containing many lymphocytes, large mononuclears and fibroblasts. In 1 case the walls of the thickened veins near a chronic pulmonary abscess contained many polymorphonuclears. In 4 cases the walls of some small veins were infiltrated by tumor cells. In 2 cases the thickened intima contained a few endothelium-lined lumens. In 6 cases the thickened patches were divided into elastic tissue and some of the thickened intima contained a little fine irregular superficial and deep layers by an elastic fiber.

In 3 cases, the media near chronic pulmonary abscesses or active foci of tuberculosis showed infiltration with lymphocytes, large

TABLE 15.—*Distribution of Sclerosis of Large Intrapulmonary Veins According to Age and Sex*

Age, Years	Males				Females			
	No. of Patients	Patients with Sclerosis		Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis		Average Degree of Sclerosis
		Number	Percent- age			Number	Percent- age	
0-9	1	0	..	0	2	0	..	0
10-19	8	2	25	0.8+	0
20-29	3	1	..	0.3+	2	0
30-39	4	2	..	1.0+	0
40-49	7	3	43	0.9+	5	1	..	0
50-59	13	8	62	1.0+	3	2	40	2.0+
60-69	12	9	75	1.0+	7	2	..	0.4+
70-79	3	1	..	1.0+	8	2	29	0.7+
80-89	0.3+	7	6	75	0.5+
Totals*	51	26	52	0.9+	36	19	53	0.8+

* Of the total number of 87 patients, 45 (52 per cent) showed sclerosis of the large intrapulmonary veins (average degree 0.8+). Of the 25 patients less than 40 years of age, 8 (32 per cent) showed sclerosis (average degree, 0.7+). Of the 62 patients over 40 years of age, 37 (60 per cent) showed sclerosis (average degree, 0.9+).

mononuclears and sometimes polymorphonuclears. In 1 case in the "cardiac disease" group the media was notably thick and muscular. Apart from the presence of inflammatory changes in the walls of veins near abscesses or foci of tuberculosis, the chief differences in the various etiologic groups were that in some cases of heart disease (usually with congestive failure) the thickened intima contained elastic tissue, which was unusual in other groups, and that in 1 case of congestive failure the media was thick and muscular.

Large Intrapulmonary Veins.—Sclerosis of the veins more than 1 mm. in external diameter, contrary to the statements of Ljungdahl^{17c} and Moschowitz,²¹³ was found to be much less common and less severe than that of the small veins (tables 15 and 16). Sclerosis was present in 45 of 87 cases (52 per cent) and was equally common in males and females. Sclerosis was present in 8 of 25 patients under 40 (32 per cent) and in 37 of 62 over 40 (60 per cent).

As these veins are usually collapsed after death, it is impossible to measure their external diameter accurately, and the thickness of the intima was expressed as a percentage of the thickness of the wall excluding the adventitia. The presence of any connective tissue between the endothelium and the elastica interna was taken as evidence of sclerosis. If the average thickness of the intima was less than 10 per cent of the thickness of the wall of the vein, the sclerosis was graded +; from 10 to 30 per cent, ++; if from 30 to 50 per cent, +++, and if over 50 per cent, ++++.

Table 16 shows that there is a tendency for sclerosis of the large veins to increase with the age of the patient even in the absence of factors thought to raise the pulmonary arterial pressure. The sclerosis was increased in frequency, though not appreciably in severity, in the presence of chronic pulmonary disease and in the presence of cardiac disease, alone or with pulmonary disease, and especially if congestive heart failure was present the sclerosis is increased both in frequency and in severity. In the "no cause" group there was slight patchy thickening of the intima in 2 of the 15 patients under 40 and slight uniform thickening in 1. Of the 15 patients over 40, 4 showed slight patchy intimal thickening, and 2, in whom the adventitia showed deposits of tumor, showed fairly marked thickening. In the "cardiac disease" group both patients under 40, who died of congestive heart failure, showed marked thickening of the intima of all the large veins. There was only slight patchy thickening in 2 of the 3 patients over 40, none of whom had congestive heart failure. In the "pulmonary and cardiac disease" group both patients under 40 had congestive heart failure and both showed slight or marked intimal thickening of the large veins.

The histologic picture was similar to that found in the arteries. There was patchy or uniform thickening of the intima of few or many veins in the affected patients. The intimal connective tissue was usually dense and almost acellular, but in 2 cases, near foci of active tuberculosis, it was loose and fibrillar and contained numbers of lymphocytes. Fat was rarely present, being observed both in foam cells and loose in the intimal connective tissue only in the 2 patients under 40 with cardiac disease. Smooth muscle cells were also rare, being noted only in 2 cases. In 1 patient (a boy of 11 with rheumatic heart disease, fibrosis of the lungs and heart failure) many of the veins showed marked uneven intimal thickening by dense, pink-staining connective tissue, in which were many groups of longitudinally directed muscle cells. Numbers of endothelium-lined lumens were present in the thickened intima in 2 cases near foci of active tuberculosis. Elastic tissue was unusual, being observed in only 4 patients, 3 of whom died of congestive heart failure. Occasionally the elastica interna was frayed, fragmented or missing.

TABLE 16.—Distribution of Sclerosis in Large Intrapulmonary Veins According to Age, Sex and Etiologic Factor*

Etiologic Factor	Age, Years	Males						Females					
		Patients with Sclerosis				Thickness of Intima	Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis		Thickness of Intima	Average Degree of Sclerosis	
		No. of Patients	Number	Percentage	Number				Percentage				
No cause	0-39 40-89	8 10	1 5	13 50	1 (0-7) 5 (0-19)	0.1+ 0.8+	7 5	2 1	29 20	2 (0-8) 1 (0-1)	0.3+ 0.2+		
Pulmonary disease	0-39 40-89	4 7	1 4	25 57	2 (0-6) 10 (0-35)	0.3+ 1.0+	.. 11	.. 10	.. 91	.. 9 (0-30) 1.3+		
Cardiac disease	0-39 40-89	1 2	1 1	39 5 (0-10)	3.0+ 0.5+	1 1	1 1	52 3	4.0+ 1.0+		
Hypertension	0-39 40-89	.. 2	.. 1 3 (0-6) 0.5+	1 4	0 1	0 1 (0-5)	0 0.3+		
Pulmonary and cardiac disease	0-39 40-89	2 8	2 6	.. 75	25 (10-39) 16 (0-30)	2.0+ 2.3+	.. 2	.. 2 20 (18-22) 2.0+		
Cardiac disease and hypertension	0-39 40-89	.. 1	.. 1 13 2.0+	.. 1	.. 0 0 0		
Pulmonary and cardiac disease and hypertension	0-39 40-89	.. 2	.. 1 5 (0-11) 1.0+	.. 1	.. 0 0 0		
Pulmonary disease and hypertension	0-39 40-89	.. 2	.. 1 5 (0-10) 0.5+	.. 3	.. 2 10 (0-19) 1.0+		

* The thickness of the intima is expressed as a percentage of the thickness of the wall of the vessel exclusive of the adventitia. Where measurements are given, the first figure is the average and the figures in parentheses represent the extremes.

The media was notably thick and muscular in 20 patients, 9 of whom died of congestive heart failure. In 1 case it was invaded by lymphocytes and capillaries near foci of active tuberculosis. In 1 case the media was invaded by carcinoma cells, and in another, in which there were deposits of carcinoma in the adventitia, the media was infiltrated by lymphocytes and large mononuclears.

Apart from inflammatory changes in veins near tuberculous foci, the chief differences in the etiologic groups are that the intimal thickening was greatest in the cases in the "cardiac disease" and "pulmonary and cardiac disease" groups in which there was congestive heart failure. In these cases the thickened intima often contained fat, smooth muscle cells

TABLE 17.—*Size of the Main Extrapulmonary Pulmonary Veins in the Various Etiologic Groups*

Etiologic Factor	Circumference of the Stem of the Pulmonary Artery, Cm.	Circumference of the Pooled Pulmonary Veins,* Cm.	Circumference of the Pulmonary Veins Expressed as a Percentage of the Diameter of the Stem	Cross-Sectional Area of the Pulmonary Veins, Percentages†
No cause	7.5 (5.8-9.1)	5.7 (4.1-7.8)	76 (62-89)	68 (50-81)
Pulmonary disease	7.8 (6.4-9.0)	6.2 (4.9-8.0)	77 (58-91)	68 (52-71)
Cardiac disease	8.0 (7.3-9.0)	6.0 (5.3-6.7)	73 (65-84)	55 (49-60)
Hypertension	8.5 (6.5-10.3)	6.0 (4.5-8.0)	69 (61-85)	50 (37-61)
Pulmonary and cardiac disease	8.0 (6.8-9.7)	6.9 (5.2-9.7)	88 (79-141)	90 (61-196)
Cardiac disease and hypertension	9.6 (9.2-10.3)	7.3 (6.1-9.1)	76 (67-88)	56 (45-78)
Pulmonary and cardiac disease and hypertension	8.3 (7.7-8.8)	7.6 (4.9-10.5)	91 (64-124)	91 (35-142)
Pulmonary disease and hypertension	8.3 (6.5-10.2)	6.5 (5.0-7.7)	80 (75-87)	61 (57-66)
Congestive heart failure	8.8 (6.8-10.3)	7.6 (5.6-10.5)	87 (69-141)	90 (50-196)

* By the circumference of the pooled pulmonary veins is meant the circumference of a single vessel of the same cross-sectional area as the four pulmonary veins together.

† The cross-sectional area of the pulmonary veins is expressed as a percentage of the cross-sectional area of the stem of the pulmonary artery.

and elastic tissue, which were not present in the other groups and thickening and muscularity of the media were commoner in these cases than in the others.

Main Extrapulmonary Pulmonary Veins.—These were examined in only the last 38 cases of the series. Sclerosis was never seen with the naked eye. Table 17 shows the size of the main pulmonary veins in the various etiologic groups. Normally, if the four pulmonary veins had been joined to form a single vessel of the same cross-sectional area as the four combined, this vessel would have had a circumference of from 4.1 to 7.3 cm. (average, 6.3 cm.); this is equivalent to from 69 to 93 per cent (average, 78 per cent) of the circumference of the corresponding stem of the pulmonary artery, and to from 48 to 86 per cent (average, 61 per cent) of the cross-sectional area of the stem of the pulmonary artery in each case. The table shows that the veins were dilated in the

"pulmonary and cardiac" disease and "pulmonary and cardiac disease and hypertension" groups, which contained cases of congestive heart failure. This is also shown if all the cases of congestive heart failure are collected together. In 2 of these cases the capacity of the veins was much greater than that of the stem of the pulmonary artery.

Table 18 shows that although sclerosis was never seen macroscopically it was observed microscopically in 25 cases (66 per cent). The presence of any connective tissue between the endothelium and the elastica interna was taken as evidence of sclerosis. If the thickness of the wall of the vein, exclusive of the adventitia, the sclerosis was graded +; if it was from 0.1 to 0.2 mm. thick, or from 20 to 50 per cent of the

TABLE 18.—Distribution of Sclerosis of the Main Extrapulmonary Pulmonary Veins According to Age and Sex

Age, Years	Males			Females		
	Number of Patients	Patients with Sclerosis	Average Degree of Sclerosis	Number of Patients	Patients with Sclerosis	Average Degree of Sclerosis
0-9	3	0	0
10-19	1	1	1.5+	1	..	0
20-29	2	0	0	2	1
30-39	5	1	1.0+	0	0	3.0+
40-49	5	4	1.0+	1	1	0
50-59	5	4	1.6+	2	2	1.0+
60-69	2	4	1.6+	1	1	0.7+
70-79	..	2	1.6+	3	3	0.5+
80-89	2.0+	1	1	2.0+
Totals*.....	22	16 (73 per cent)	1.4+	10 (57 per cent)	9	1.0+

* Of the total number of 38 patients, 25 (66 per cent) showed sclerosis of the main extrapulmonary pulmonary veins (average degree, 1.2+). Of the 11 patients less than 40 years of age, 3 (27 per cent) showed sclerosis (average degree, 0.7+). Of the 27 under 40 years of age, 22 (82 per cent) showed sclerosis (average degree, 1.4+).

thickness of the wall, ++, and if it was over 0.2 mm., or over 50 per cent of the thickness of the wall, +++. Of 11 patients under 40 sclerosis was present in 3 (27 per cent), while of 27 patients over 40 sclerosis was present in 22 (82 per cent).

Table 19 shows that sclerosis is uncommon and slight in patients under 40 but that it is rather commoner, though still slight, in those over 40, in the absence of factors that are thought to raise the pulmonary arterial pressure. The presence of pulmonary or cardiac disease or both increased the frequency and severity of the sclerosis of the main pulmonary veins in patients both over and under 40, particularly in patients with congestive heart failure. The increased frequency and severity in patients with chronic pulmonary disease are noteworthy, since there the pressure in the pulmonary veins might be expected, if anything, to be reduced, as the abnormal resistance to the pulmonary circulation is provided by the capillaries.

TABLE 19.—*Distribution of Sclerosis of the Main Extrapulmonary Pulmonary Veins According to Age, Sex and Etiologic Factor **

Etiologic Factor	Age, Years	Males					Females				
		No. of Patients	Patients with Sclerosis	Thickness of Intima,† Percentage	Thickness of Media, Mm.	Average Degree of Sclerosis	No. of Patients	Patients with Sclerosis	Thickness of Intima,† Percentage	Thickness of Media, Mm.	Average Degree of Sclerosis
No cause	0-39	1	0	0	0.224	0	3	1	5 (0-16)	0.277 (0.232-0.319)	0.3+
	40-89	4	2	12 (0-33)	0.307 (0.166-0.448)	0.7+	1	1	20	0.299	1.0+
Pulmonary disease	0-39	2	0	0	0.108 (0.083-0.133)	0	1	0	0	0
	40-89	7	6 (86%)	18 (0-65)	0.228 (0.059-0.493)	1.3+	5	3 (60%)	12 (0-23)	0.220 (0.116-0.332)	0.8+
Cardiac disease	0-39	1	1	40	0.266	2.0+
	40-89	1	1	20	0.232	2.0+
Hypertension	0-39
	40-89	2	1	24 (0-48)	0.249 (0.083-0.415)	1.0+
Pulmonary and cardiac disease	0-39	2	2	40 (36-44)	0.453 (0.285-0.581)	2.0+
	40-89	2	2	27 (13-61)	0.216 (0.183-0.270)	1.5+	1	1	13	0.137	1.0+
Cardiac disease and hypertension	0-39
	40-89	1	1	28	0.249	2.0+
Pulmonary and cardiac disease and hypertension	0-39
	40-89	1	1	27	0.499	2.0+	1	1	2	0.325	1.0+
Pulmonary disease and hypertension	0-39
	40-89	1	1	50	0.232	3.0+	1	1	60	0.249	3.0+

* When measurements are given, the first figure represents the average and the figures in parentheses represent the extremes.

† The thickness of the intima is expressed as a percentage of the thickness of the wall of the vein exclusive of the adventitia.

The histologic changes (fig. 8) were similar to those in the arteries. There was patchy or uniform thickening of the intima by connective tissue, which was usually dense and almost acellular and stained pink with Van Gieson's stain. In 2 cases there were foci of lymphocytes in the thickened intima. In 1 case the thickened intima contained fat both in foam cells and lying free. A little fine elastic tissue was present in 8 cases, and in 1 case there was a great deal of irregular elastic tissue. In 1 case (that of a woman with active rheumatic heart disease) there were foci of lymphocytes not only in the intima but also in the media and adventitia.

Muscularity of the Veins.—No measurements were possible of the amount of muscle in the media of the main intrapulmonary and extra-

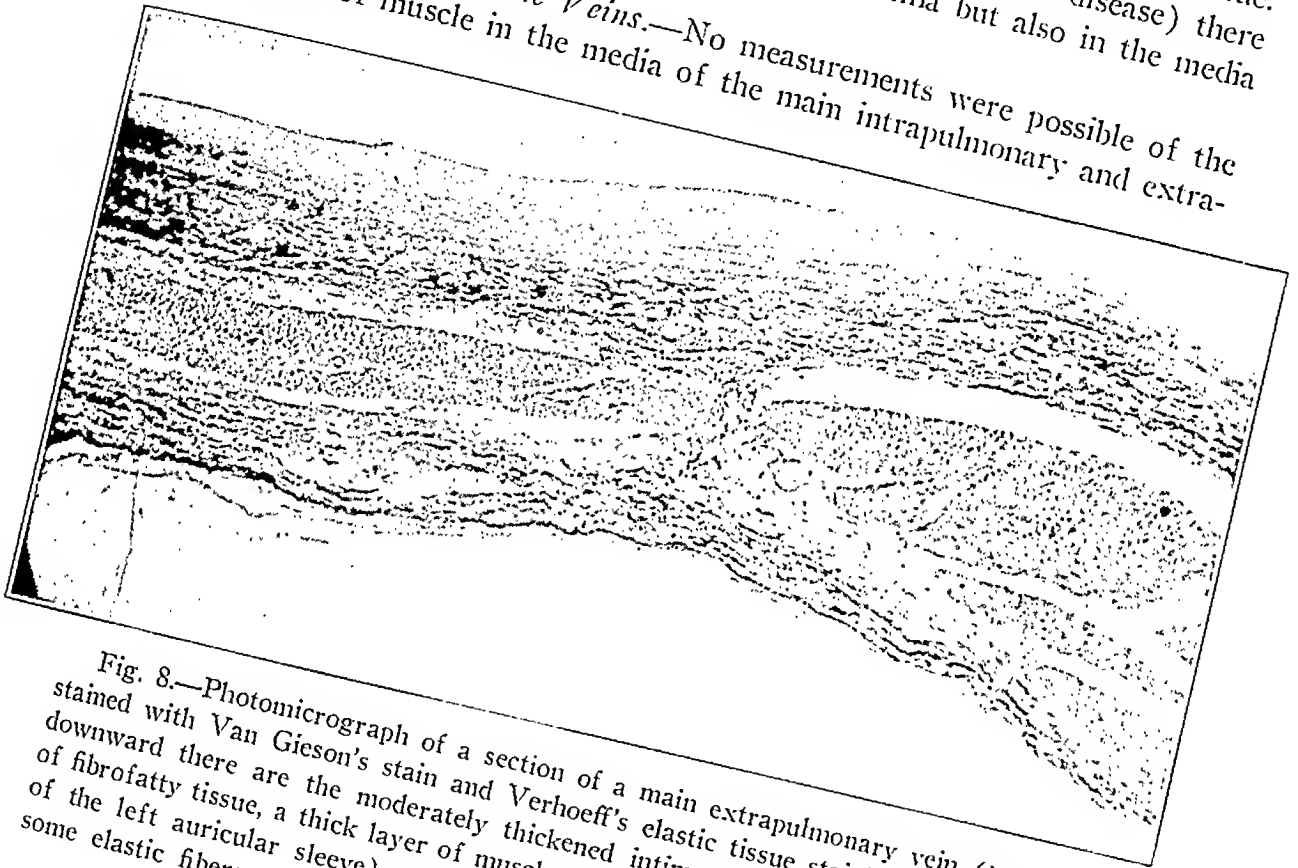


Fig. 8.—Photomicrograph of a section of a main extrapulmonary vein ($\times 20$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). From above downward there are the moderately thickened intima, the media, a narrow zone of fibrofatty tissue, a thick layer of muscle, including heart muscle (at the junction of the left auricular sleeve) and the adventitia consisting of fibrous tissue with some elastic fibers.

pulmonary veins, as it was usually irregularly scattered. The muscularity was graded as "little" when there were only a few muscle fibers in the medial connective and elastic tissue, this probably representing the normal; "moderate" when muscle formed from one fourth to one half of the media (this is perhaps excessive, though it may represent the upper limit of the normal), and "excessive" when most of the media consisted of muscle and thick strands of smooth muscle, distinct from the sleeve of cardiac muscle, were also present in the adventitia. Excessive muscularity was present in 22 of 84 cases (26 per cent) and showed

no appreciable difference with age or sex (table 20). Table 21 shows that excessive muscularity was commonly present in patients with heart disease, either with or without pulmonary disease and hypertension,

TABLE 20.—*Distribution of the Muscularity of the Large Intrapulmonary and Extrapulmonary Pulmonary Veins According to Age and Sex*

Age, Years	Males				No. of Patients	Females			
	No. of Patients	Degree of Muscularity*				No. of Patients	Degree of Muscularity*		
		Little	Moderate	Excessive			Little	Moderate	Excessive
0- 9	1	1	3	3	
10-19	9	7	..	2	
20-29	1	..	1	..	1	1	
30-39	4	1	2	1	4	2	1	1	
40-49	7	4	2	1	3	2	..	1	
50-59	13	4	4	5	7	5	2	..	
60-69	12	6	3	3	8	5	1	2	
70-79	4	..	2	2	5	3	..	2	
80-89	2	1	..	1	
Totals†	51	23	14	14	33	21	4	8	
				(27 per cent)				(24 per cent)	

* The terms little, moderate and excessive refer to the estimated amount of muscle in the walls of the veins and are defined in the text.

† Of the 84 patients, 44 showed little, 18 moderate and 22 (26 per cent) excessive muscularity. Of the 23 patients less than 40 years of age, 14 showed little, 4 moderate and 5 (22 per cent) excessive muscularity. Of the 61 patients over 40 years of age, 30 showed little, 14 moderate and 17 (28 per cent) excessive muscularity.

TABLE 21.—*Distribution of Muscularity of the Large Intrapulmonary and Extrapulmonary Pulmonary Veins According to Age and Etiologic Factor*

Etiologic Factor	Age, Years	No. of Patients	Degree of Muscularity*		
			Little	Moderate	Excessive
No cause	0-39	13	11	1	1
	40-89	14	10	4	..
Pulmonary disease	0-39	4	2	1	1
	40-89	18	12	3	3
Cardiac disease	0-39	2	2
	40-89	3	..	1	2
Hypertension	0-39	1	1
	40-89	6	4	1	1
Pulmonary and cardiac disease	0-39	3	..	2	1
	40-89	10	1	4	5
Cardiac disease and hypertension	0-39
	40-89	2	2
Pulmonary and cardiac disease and hypertension	0-39
	40-89	3	1	..	2
Pulmonary disease and hypertension	0-39
	40-89	5	2	1	2

* The terms little, moderate and excessive refer to the estimated amount of muscle in the walls of the veins and are defined in the text.

particularly if heart failure was present. It is possible that the increased muscularity might be an adaptation to an increased pressure in the pulmonary veins, though a similar excessive muscularity was sometimes present in patients without heart disease or heart failure and even in patients with chronic pulmonary disease in whom the pressure in the

pulmonary veins might be expected to be below normal. However, the great frequency of excessive muscularity in patients with heart disease with or without pulmonary disease and hypertension (15 of 21 patients, or 71 per cent, compared with 7 of the remaining 63 patients, or 11 per cent) seems too marked to be accidental.

Systemic Vessels.—These were examined macroscopically and microscopically in every case, particularly the aorta and the coronary, renal and splenic vessels. Various grades of sclerosis were found in 92 of the 100 patients, the exceptions all being in patients under 40. Syphilitic aortitis was found in 9 cases. There was no correlation between the changes in the systemic and pulmonary vessels except that in both it was evident that sclerosis increased in frequency and severity with age.

(To be continued)

URTICARIA DUE TO SENSITIVITY TO COLD

SURVEY OF THE LITERATURE AND REPORT OF A CASE, WITH EXPERIMENTAL OBSERVATIONS

HAROLD D. LEVINE, M.D.

BOSTON

Attention has recently been drawn to the occasional occurrence of sensitivity to such physical agents as heat, cold or pressure. Patients with such sensitivity react to the local stimulus with an urticarial wheal and may in addition show a general constitutional reaction. Duke¹ in this country has devoted particular attention to this subject. Cases falling in this category have been reported with increasing frequency, especially in the German literature. Investigation of the mechanism of these reactions has yielded many interesting facts, many of them at marked variance with one another, but the etiology has not yet been determined. Many writers have considered the reaction to be allergic or immunopathologic, others, the result of alteration of the colloidal state of the blood and others, the result of altered mechanism of the central nervous system or of peripheral neurovascular mechanisms. Urbach and Fasal,² impressed with the conflicting mass of data on the subject, have considered that the etiology is not unitary but may be the result of changes in one sort of mechanism in one case and of another mechanism in another. They have stressed the need of a careful study of the individual case and have advised that therapy be based on the results obtained.

Cases of sensitiveness to cold as described in the literature have been divided into several classes. In the first group fall cases in which a purely local sensitivity is exhibited without an accompanying general, constitutional or systemic reaction. The second group comprises cases

From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Duke, W. W.: (a) Heat and Effort Sensitiveness: Cold Sensitiveness; Relationship to Heat Prostration, Effort Syndrome, Asthma, Urticaria, Dermatoses, Noninfectious Coryza and Infections, *Arch. Int. Med.* **45**:206 (Feb.) 1930; (b) Clinical Manifestations of Heat and Effort Sensitiveness: Relationship to Heat Prostration, Effort Syndrome, Asthma, Urticaria, Dermatoses, Noninfectious Coryza and Infections, *J. Allergy* **3**:257, 1932; (c) Treatment of Heat and Effort Sensitiveness and Cold Sensitiveness and Treatment of Contact Urticaria Caused by Light, Cold and Scratches, *ibid.* **3**:408, 1932; (d) Relationship of Heat and Effort Sensitiveness and Cold Sensitiveness to Functional Cardiac Disorders Including Angina Pectoris, Tachycardia and Ventricular Extrasystoles, *ibid.* **4**:38, 1932.

2. Urbach, E., and Fasal, F.: Vasoallergie oder Vasoneuropathie als Ursache von Kälte-, Wärme- und Druckurtikaria? Ein Beitrag zur Pathogenese und Therapie der sogenannten physikalischen Allergien der Haut, *Wien. klin. Wchnschr.* **46**:1069, 1933.

in which there is a local reaction with an accompanying systemic reaction. In this group the constitutional symptoms may appear following the exposure of small and restricted areas, but more often the local whealed area must be extensive before a general reaction is elicited. Persons showing no general reaction on exposure of a small area to cold may show such a response when a larger area is exposed. Duke inferred the existence of a third group in which a systemic or remote reaction occurred on local stimulation but without a local reaction.

In cases of the first group, that is, those in which there is a purely local reaction, the patient notices after a varying period following exposure to cold that the erythema which occurs in normal persons gives way to a wheal, sharply limited to the exposed area and accompanied by itching and burning. Harris, Lewis and Vaughan³ and Horton and Brown⁴ found that the reaction does not occur as long as the part is kept in contact with cold but appears a short time after removal from that contact. Freund⁵ has noted the occurrence of local reactions after almost unbelievably long latent periods following exposure to cold. The wheal may be transient or may last several hours or longer. In most of the cases reported the patient showed sensitivity of this type over the entire cutaneous area, but a few showed sensitivity on only certain areas of the skin,⁶ and some reacted more strongly on one part than another. Some patients show a sensitivity of the buccal or pharyngeal mucosa. As a rule the patient is aware of his own sensitivity, but in rare instances it is only accidentally discovered.⁷ The swelling of the hands may be so marked as to interfere with movement of the fingers. The patient's face may be so sensitive that after exposure to a cold wind the eyes may be partially closed or the features indistinguishable.^{1b} The symptoms commonly have their onset after swimming,⁸ after bath-

3. Harris, K. E.; Lewis, T., and Vaughan, J. M.: Hemoglobinuria and Urticaria from Cold Occurring Singly or in Combination; Observations Referring Especially to the Mechanism of Urticaria with Some Remarks upon Raynaud's Disease, *Heart* **14**:305, 1927.

4. Horton, B. T., and Brown, G. E.: Systemic Histamine-Like Reactions in Allergy Due to Cold, *Am. J. M. Sc.* **178**:191, 1929; *J. Allergy* **1**:193, 1929.

5. Freund, E.: Ueber Latentz und Spätreaktion nach Kälteschädigung, *Ztschr. f. d. ges. phys. Therap.* **32**:163, 1926.

6. (a) Musger, A.: Quoted by Urbach and Fasal.² (b) Bernstein, T.: Zum allergischen Charakter der Kälteurtikaria, *Dermat. Ztschr.* **64**:242, 1932.

7. Fraser, T. R.: Urticaria e Frigore, *Tr. Med.-Chir. Soc. Edinburgh* **25**:90, 1905.

8. (a) Netter: *Bull. et mém. Soc. méd. d. hôp. de Paris* **45**:339, 1921. (b) Lehner, E.: Kälteurtikaria, *Klin. Wchnschr.* **8**:306, 1929. (c) Graszi: Zur Frage des Badetodes, *München. med. Wchnschr.* **79**:1469, 1932. (d) Thannhauser, S. J.: Zur Frage des Badetodes, *ibid.* **79**:1890, 1932. (e) zum Busch, J. P.: Ueber plötzlichen Tod im kalten Bade, *Deutsche med. Wchnschr.* **59**:15, 1933. (f) Affolter, J.: Urticaria et syncope "a frigore," *Schweiz. med. Wchnschr.* **63**:881, 1933.

ing⁹ or washing in cold water,¹⁰ after being out in a cold wind or snow and after eating ice cream¹¹ or drinking cold liquids. Often, as noted by Duke, the condition is first noted after an acute illness. Duke was also impressed with the fact that the reaction is inhibited during febrile illnesses, during an artificially induced fever and following exercise and in the early morning hours. He expressed the opinion that patients with a reaction of this type are hypersusceptible to infection. They are as a rule very active. Duke and Bray¹² noted that such persons have a constantly subnormal and irregular temperature. In a long-standing case a recurrent form of eczema may be established, with seasonal exacerbations.¹³

In the second group of cases, either simultaneous with^{1b} or after a latent period of a few minutes following⁴ the appearance of the wheal there occurs a systemic reaction characterized by a fall in blood pressure,¹⁴ a sharp rise in the pulse rate,^{8f} flushing of the face and ears and a tendency to syncope^{8f} with recovery after a variable period of time. There may be headache, rigor, dyspnea, cough, generalized aches and pains or transient blindness.¹⁵ There may or may not be associated hemoglobinuria,¹⁶ and this seems more likely to occur in persons with syphilis.¹⁷ Several German authors¹⁸ have suggested that many of the accidents by drowning which occur each year even to excellent swimmers may be explained by sensitivity to cold. Tests carried out

9. Negel: Oedèmes éphémères de nature arthritique, *Progrès méd.* **12**:846, 1884. Netter.^{8a}

10. Schlenker, H.: Zur Behandlung der Kälte-Anaphylaxie, München. med. Wchnschr. **80**:974, 1933.

11. (a) Blachez: Procès-verbal de la séance du 8 Nov. 1872, *Bull. et mém. Soc. méd. d hóp. de Paris* **9**:270, 1872. (b) Wallace, T. I.: A Case of Bronchial Asthma Accompanied with Urticaria Brought on by Eating Ice Cream, *Australasian M. Gaz.* **28**:436, 1909. Lehner.^{8b}

12. Bray, G. W.: A Case of Physical Allergy: A Localized and Generalized Allergic Type of Reaction to Cold, *J. Allergy* **3**:367, 1932.

13. Bernstein, F.: Beiträge zu den physikalischen Idiosynkrasien der Haut: III. Kälteekzem, *Arch. f. Dermat. u. Syph.* **168**:103, 1933. Duke.¹⁶

14. (a) Ito, M., and Kobayashi, E.: Un cas d'urticaire par le froid chez un hérédosyphilitique, *Jap. J. Dermat. & Urol.* **30**:87, 1930. (b) Riehl, G., Jr., and Risek, E.: Zur Pathogenese der Kälteurticaria und ihrer Zusammenhänge mit der paroxysmalen Hämoglobinurie, *Ztschr. f. klin. Med.* **124**:29, 1933. (c) Horton and Brown.⁴ Bray.¹² Affolter.^{8f} Wilder^{15a} described a rise in blood pressure in his case.

15. (a) Wilder, J.: Kälteurtikaria mit schweren Allgemeinerscheinungen, *Wien. klin. Wchnschr.* **45**:1458, 1932. (b) Urbach, E., in discussion on Wilder.

16. Harris, Lewis and Vaughan.³ Riehl and Risek.^{14b}

17. (a) Moss, W. L.: Paroxysmal Hemoglobinuria: Blood Studies in Three Cases, *Bull. Johns Hopkins Hosp.* **22**:238, 1911. Numerous additional references are contained in the article by Harris, Lewis and Vaughan.³ (b) Forrest, R. W.: Case of Paroxysmal Haematuria, *Glasgow M. J.* **11**:421, 1879.

18. Lehner.^{8b} Graszl.^{8c} Urbach.^{15b} Thannhauser.^{8b} Bernstein.^{6b} Zum Busch.^{8e} Affolter.^{8f}

on subjects surviving these accidents showed them to react to cold in the same way as patients in the second group.

In the third group fall numerous cases of bronchial asthma,^{11b} vasomotor rhinitis and conjunctivitis, photophobia, abdominal pain, erythema, pruritus, urticaria, angioneurotic edema, eczema and shock, conditions believed by Duke^{1a} to be caused in some patients specifically and solely by the physical action of cold. He commented on the well known association of exposure to cold and anginal attacks and described a case in which ventricular extrasystoles could be brought on by cold and inhibited by heat.

At least three major lines of investigation have been followed in the elucidation of the etiology of these reactions. The first has been immunologic, concerning antigen-antibody reactions; the second, humoral, concerning the liberation of certain chemical substances, and the third, neurovascular, concerning altered nervous or vascular mechanisms.

THE IMMUNOLOGIC HYPOTHESIS

The method of passive transfer as worked out by Prausnitz and Küstner has been used to test immunologic specificity. Blood is removed from a vein of the arm of a patient at the height of the local and systemic reaction caused by cold, and the serum is separated and injected intracutaneously into a normal nonallergic person. The slight swelling from the injection is allowed to subside. Then cold is applied, and a wheal appears. Serum treated similarly from a normal person causes no wheal. Positive results were obtained by Harris, Lewis and Vaughan,³ Covisa and Prieto,¹⁹ Lehner,²⁰ Lehner and Rajka,²¹ Liebner²² and Bernstein^{6b} among others. Jadassohn and Schaaf,²³ Perutz, Brügel and Grünfeld,²⁴ Klein,²⁵ Marquardt,²⁶ Benjamin²⁷ and others were unable to obtain the Prausnitz-Küstner reaction in their cases.

19. Covisa, J. S., and Prieto, J. Gay: Contribucion al estudio de la urticaria al frio, *Dermat. Wchnschr.* **91**:1188, 1930.

20. Lehner, E.: *Zentralbl. f. Dermat.* **41**:199, 1932; quoted by Urbach and Fasal.² Lehner.^{8b}

21. Lehner and Rajka: *Arch. f. Dermat.* **158**:402, 1929; quoted by Urbach and Fasal.²

22. Liebner: *Zentralbl. f. Dermat.* **34**:406, 1930; quoted by Urbach and Fasal.²

23. Jadassohn, W., and Schaaf, F.: *Kälteurticaria bei zwei Geschwistern*, *Dermat. Wchnschr.* **86**:565, 1928.

24. Perutz, A.; Brügel, S., and Grünfeld, R.: *Zur Pathogenese der Kälteurticaria*, *Klin. Wchnschr.* **8**:1999, 1929.

25. Klein, A. E.: *Zur Frage der durch Wärme und Kälte ausgelösten Urtikaria*, *Dermat. Wchnschr.* **95**:1741, 1932.

26. Marquardt, F.: *Untersuchungen bei Kälteurticaria und Urticaria factitia*, *Dermat. Wchnschr.* **96**:261, 1933.

27. Benjamin, C. E.: *Zes Gevallen von Koude-Allergie*, *Nederl. tijdschr. v. geneesk* **77**:4461, 1933.

Harris, Lewis and Vaughan³ demonstrated in the serum of a patient showing both urticaria due to cold and paroxysmal hemoglobinuria the presence of a hemolytic amboceptor and a dermolytic amboceptor. They believed the response of the skin to cooling in the Prausnitz-Küstner test to be due to the presence of a dermolysin in the patient's blood; this unites with the skin at a low temperature only, and the reaction occurs after the skin is rewarmed. Their conception is that just as the hemolysin combines with the red blood cell membrane at a low temperature with subsequent alteration of its permeability so that the hemoglobin content of the cell is liberated into the serum, so does the dermolysin combine with the cutaneous cell at a low temperature, causing change in its permeability and thus bringing about the release of the contents of the cell into the intercellular medium.

The phenomenon of specific exhaustion is also invoked as attesting the immunologic nature of these reactions. After the reaction once produced has subsided, reapplication of the same stimulus—cold—for the same period becomes less and less capable of producing a wheal, while the immediately adjacent and previously untouched skin is reactive. This observation forms the basis for therapy by specific desensitization advocated by many writers.²⁸ By daily immersion of the parts in cold water of decreasing temperature for increasing periods, excellent results have been reported.

The specificity of the reaction has also been regarded as favoring its immunologic nature. In cases of sensitivity to physical agents symptoms as a rule are caused specifically by one physical agent only,³ although occasionally by two or more.²⁹ Patients sensitive to material substances rarely react specifically to the action of physical agents, and vice versa. Harris³⁰ found that of several patients with urticaria due to specific factors, such as light, cold or cat, none had a dermatographic wheal when skin was stroked; that is, none were sensitive to mechanical stimulation.

Another line of reasoning is the similarity of these phenomena to allergic or anaphylactic reactions which have been considered immune reactions. Numerous investigators, particularly the French and Italian,³¹

28. (a) Schutz, J.: Mittheilungen über eine häufiger vorkommende Form von Urtikaria chronica recidiva, München. med. Wchnschr. **42**:798, 1895. Duke.^{1c}
 (b) Vallery-Radot, P., and Blamoutier, P.: Urticaire par le froid: Traitement par l'accoutumance, Bull. et mém. soc. méd. d. hôp. de Paris **47**:1907, 1931.

29. Henry, J. P.: J. Allergy **1**:194, 1929. Duke.^{1a}

30. Harris, K. E.: Urticaria: Observations upon the Vascular Reactions in the Skin, Quart. J. Med. **24**:347, 1931.

31. Gougerot; Peyre, Moutet and Bourdillon: Urticaire par le froid, Bull. Soc. franç. de dermat. et syph. **34**:321, 1927. Joltrain, E.; Morat, D., and Ley, J.: Urticaire géante: Observée chez un morphinomane à chaque tentative de sevrage, Presse méd. **35**:1361, 1927. Covisa and Prieto.¹⁹ Marquardt.²⁶ Urbach and Fasal.²

have been able to follow the lead of Widal and his associates³² and have shown that these reactions, like anaphylactic responses in general, are characterized by an abrupt fall in the leukocyte count. Other workers could not demonstrate this so-called hemoclastic crisis,³³ and Lehner^{3b} found that instead of falling the white blood cell count rose. Eosinophilia has occasionally been observed in these cases.³⁴ Bray¹² stated that eosinophilia is rare, but he was able to demonstrate local eosinophilia in a wheal due to sensitivity to cold. An instance of familial occurrence of the condition was described by Jadassohn and Schaaf.³⁵ Bray's patient had a strong family history of asthma, while the patient described by Widal, Abrami and Lermoyez³² later had nasal polyps and asthma.

THE HUMORAL HYPOTHESIS

Harris, Lewis and Vaughan found the reaction to cold to be of the usual type seen in cases of cutaneous injury, namely, an acute triple response with local dilatation of arterioles, venules and capillaries followed by the formation of wheals and the surrounding flare due to arteriolar dilatation caused by a local axon reflex. They explained the systemic reaction following the local response as the result of the diffusion of a histamine-like substance into the blood stream by which it is carried to remote parts of the body. These workers, as well as Horton and Brown,⁴ Lehner and Rajka²¹ and Bray,¹² were able to show that with a tourniquet applied so as to cut off the venous return from the hand or the arterial supply to the hand before it was immersed in the cold water and kept on for an additional period after the hand was removed from the cold environment a local response was produced but a systemic reaction did not occur. When the tourniquet was released the systemic reaction took place. Horton and Brown³⁵ adduced further evidence in favor of the release of a histamine-like body in a patient in whom a rise in the free acidity of the gastric juice from 0 to 54 units followed the local reaction. The effective treatment by Bray¹² of his patient with sensitivity to cold, in whom he was able to bring about desensitization to cold by the injection of histamine, may also be pertinent. Marquardt's experience with the tourniquet test was at marked variance with the foregoing observations.²⁶ In three cases he found that a local wheal did not form if a tourniquet had previously been applied and that the wheal appeared only when the circulation was

32. Widal, F.; Abrami, P., and Lermoyez, J.: *Anaphylaxie et idiosyncrasie*, Presse méd. **30**:189, 1922.

33. Vallery-Radot and Blamoutier.^{28b} Perutz, Brügel and Schaaf.²⁴ Riehl and Risek.^{14b} Klein.²⁵

34. Affolter.^{8f} Marquardt.²⁶

35. Horton, B. T., and Brown, G. E.: Histamine-Like Effects on Gastric Acidity Due to Cold, Proc. Staff Meet., Mayo Clin. **7**:367, 1932.

restored. General reactions did not occur in his first case and were not mentioned in the reports on the other two. Duke and Wagner³⁶ found that the local and general reactions were independent of the application of the tourniquet.

THE NEUROVASCULAR HYPOTHESIS

Duke,^{1a} having found that no systemic reactions followed if heat was applied to one peripheral area while cold was applied to another area in persons sensitive to cold, concluded that the general reaction has much to do with the actual sensation of cold. He conceived of the entire condition being due to an imbalance of the mechanism for the regulation of heat. He emphasized the factors of the history of previous infection, the courses of subnormal temperature and the inhibition of the reaction during spontaneous or artificially induced fever. Wilder,^{15a} trying to carry the idea of involvement of the central nervous system one step further, found in his case of urticaria caused by cold that the suggestion of cold in hypnosis did not cause the formation of a wheal. Perutz, Brügel and Grünfeld²⁴ focused their attention on the peripheral rather than the central nervous mechanism and found that rubbing the skin of a patient with menthol, which specifically stimulates the cold receptors of the skin, either causes an abortive wheal or sensitizes the skin so that a wheal is more readily produced on the subsequent application of cold. They concluded that urticaria caused by cold is due to a vasoneurosis of the receptors of cold (peripheral nerve endings). These results have not been confirmed.

Although it is commonly stated that syphilis is a common cause of the occurrence of urticaria due to cold, a glance at the literature shows the concurrence to be infrequent. The syphilitic cases may³⁷ or may not³⁸ be associated with paroxysmal hemoglobinuria. Some cases of nonsyphilitic persons have been reported in which both hemoglobinuria and urticaria caused by cold were exhibited.^{14b}

REPORT OF CASE

History.—A housewife 36 years old was admitted to the Peter Bent Brigham Hospital on Dec. 15, 1933. She ate some sherbet late one afternoon in June. While eating it she noticed a sense of constriction in the throat. That evening she felt very sick, experienced numerous aches and pains throughout her body and had great difficulty in catching her breath. She felt the disturbance through the night and awoke at about 1 o'clock in the morning with severe pains in the back. It was very hot, and when she awoke she was uncovered. She had a moderately severe cold in the head for the next four or five days. On the fourth

36. Wagner, R.: Wind- und Kälteurtikaria bei Lues hereditaria, *Dermat. Wchnschr.* **74**:489, 1922.

37. Moss.^{17a} Forrest.^{17b} Harris, Lewis and Vaughan.³

38. Kleeberg: Kälteurtikaria, *Berl. klin. Wchnschr.* **58**:581, 1921. Wagner.³⁶ Ito and Kobayashi.^{14a}

day, feeling somewhat better, she noticed for the first time that any part of her body would swell when it touched a cold object, for example, when her feet touched the cold floor or her hands touched the cold tile of the bathroom fixtures. The swelling thus occasioned would persist for from several hours up to more than a day. This condition of sensitivity to cold persisted up to the time of admission to the hospital and was the patient's complaint on admission. Whenever her hands were exposed to cold there developed, first, a local reddening, followed by a sharply demarcated blanched swelling, bordered by a thin, fading, reddish area. This was associated with a stinging, throbbing sensation "as if all the blood in the body had rushed to the hands." The hands would remain swollen for several hours. She found that plunging the swollen hands into warm water would hasten the disappearance of the swelling. On two occasions while washing vegetables in cold water her hands became swollen to two or three times their normal size and remained so for three days. She also noticed in going outdoors on a cold day that her nose felt "hard" and "puffed." She also found that swelling and tingling of the tongue and throat developed and that she had difficulty in swallowing when she took cold solid or liquid food. About a month after the onset of the difficulty the patient ventured to go in swimming, but her body soon began to tingle, and there developed generalized small white wheals so that she had to leave the water.

It is important to note that the patient had eaten sherbet on several occasions before the apparent inciting episode, but without ill effect. The severity of the symptoms of swelling on exposure to cold seemed to have abated during the month or two preceding admission to the hospital. At first the swelling was associated with weakness, malaise and generalized aches and pains, but the patient never lost consciousness. More recently systemic reaction was less and less prone to follow.

The patient had never been sensitive to the effects of excessive heat nor had she ever had hematuria or a history suggestive of paroxysmal hemoglobinuria. There was no personal or family history of any allergic condition. The menstrual periods were always regular. She had three children, all of whom were well. Her usual weight was about 137 pounds (62.1 Kg.), and during the six months preceding admission to the hospital she gained about 5 pounds (2.3 Kg.).

Cutaneous tests done elsewhere with the common cereals, egg and milk showed the patient to react positively to barley and questionably to rye and milk, and attempts were made to desensitize her to these. Extraction of several abscessed teeth was likewise recommended and carried out. She was also told to avoid fresh fruits and vegetables, which advice she followed. Desensitization by increasing exposure to progressively colder baths was also advised.

Examination.—Physical examination on admission gave negative results except for a faint systolic murmur at the base of the heart and a reddened pharynx.

The red blood cell count was 4,150,000 per cubic millimeter; the hemoglobin content was 78 per cent (Sahli), and the white blood cell count was 10,000. A stained smear showed a differential count of 68 per cent polymorphonuclear leukocytes, 23 per cent lymphocytes, 6 per cent monocytes, 1 per cent eosinophils and 2 per cent basophils. The red blood cells and platelets were normal in appearance. Examination of the urine gave negative results. The Wassermann and Hinton reactions of the blood were negative. The stools were normal. The basal metabolic rate was — 6 per cent.

Experimental Observations.—During the patient's stay in the hospital and while she was being followed in the outdoor department numerous observations were made. It was found that urticaria followed the application of ice or water at from 0 to 20 C.

Attempts to carry out the reaction of passive transfer (Prausnitz-Küstner reaction) were unsuccessful. Blood was removed aseptically from the antecubital veins draining the hand both before and twenty-two minutes after exposure to ice-water for five minutes (nineteen minutes after the beginning of visible local swelling). The serums were separated. Neither was capable of causing formation of a wheal when it was injected into the skin of a normal person and ice was subsequently applied. The blood pressure and pulse rate were carefully followed before, during and after the immersion (table 1). Aside from a transient elevation of the blood pressure on first contact with the cold water there was essentially no change, and the patient did not complain of symptoms suggesting shock. There was likewise no significant change in the calcium and potassium content of the

TABLE 1.—*Effect of Local Reaction on the Blood Pressure, Pulse Rate, Cation Relationships and Immunologic Properties of the Blood*

Time	Observations	Blood Pressure	Pulse Rate	Calcium, Mg. per 100 Cc.*	Potassium* (mEq/l.)	Prausnitz-Küstner Reaction	Hemolytic Amboceptor
2:42	125/74	90
2:44	114/75	88
2:46	118/73	86
2:50	120/72	88
2:55	First specimen of blood withdrawn	10.2	4.1	Negative	Not present
3:00	120/80	84
3:05	Hands immersed in ice-cold water
3:06	138/92	92
3:08	Hand itched; no swelling	130/80	92
3:10	Hand was removed from water; hand was red, not swollen; patient complained of throbbing
3:11	Hand felt numb	120/80	92
3:13	Hand began to swell; felt as if "boiling"
3:15	126/83	88
3:19	122/82	86
3:28	Swelling was well marked	110/72	86
3:32	Second specimen of blood withdrawn	120/80	86	9.7	3.9	Negative	Not present
3:34	122/75	88

* These values were determined by Dr. J. C. Aub and Dr. W. T. Salter.

blood serum before and during the reaction. The local swelling did not appear until a few minutes after the hand had been removed from the cold water. This observation was confirmed several times, but the immersion was never maintained for more than ten minutes to determine whether the swelling would occur even if the hand were kept in contact with cold for a longer time. Hemoglobinuria was never produced by the local reaction, and the presence of a hemolysin in the blood before or during the reaction (the technic of Donath and Landsteiner³⁹ being employed) could not be demonstrated.

In another experiment washings were obtained from a large whealed area by repeatedly injecting and withdrawing sterile physiologic solution of sodium chloride with a 1 cc. hypodermic syringe. This material was capable of causing a persistent wheal in a neighboring cutaneous area while a control injection of physio-

39. Donath, J., and Landsteiner, K.: Ueber paroxysmale Hämoglobinurie, München. med. Wchnschr. 2:1590, 1904.

logic solution of sodium chloride failed to do so (fig. 1). Figure 1 shows the "mother" wheal and the small wheal produced by injecting the washings into the neighboring skin.

The finding of local eosinophilia as described by Bray was confirmed in the present case. Capillary blood removed from the ring finger of each hand before the reaction showed an eosinophil count of 1 per cent. After the formation of the wheal capillary blood from the right hand obtained by puncture through the wheal showed a 6 per cent eosinophil count (table 2), while the eosinophil count in blood from the unexposed hand remained at 1 per cent. Blood from a normal person's hand showed no local rise in the eosinophil count following exposure to cold. The patient showed no significant change in the remainder of the leukocyte formula, in the total white blood cell count, in the level of chloride in the venous blood or in the carbon dioxide-combining power.

TABLE 2.—Effect of Local Reaction on the Red Blood Cell Count, Distribution of Leukocytes, Chloride Content, and Carbon Dioxide-Combining Power

Location of Test	Red Blood Cells	White Blood Cells	Poly-mor-pho-nu-clears	Lym-pho-cytes	Mono-nu-clears	Eosino-phils	Baso-phils	Chlorides (Whole Venous Blood), Mg. per 100 Cc.	Chlor. Ides (Plasma), Mg. per 100 Cc.	Carbon Dioxide-Combining Power, Vols. %
Before reaction										
Right ring finger	4,160,000	7,200	56	37	5	1	1
Left ring finger	4,150,000	9,000	57	36	6	1	0
Venous blood	518	566	65.5
Twenty minutes after reaction										
Right (exposed) ring finger	3,530,000	7,400	57	35	2	0	0
Left (unexposed) ring finger	4,080,000	7,400	50	44	5	1	0
Venous blood	511	563	69.2

An attempt was made to confirm the findings of Perutz, Brügel and Grünfeld, but this was unsuccessful. Local rubbing with a 10 per cent solution of menthol in alcohol so as to produce a distinct local sensation of cold did not cause the appearance of a wheal, nor did it cause the rubbed area to react more readily than the surrounding cutaneous area to the local application of cold. It was also found that stroking the patient's skin either lightly or with heavy pressure did not cause the formation of a wheal. She was not sensitive to the local effect of heat.

Prior anesthesia of the skin with procaine hydrochloride so that ice locally applied was not felt to be cold had no influence on the subsequent development of a wheal on exposure to cold.

During her stay in the hospital the patient had a normal temperature, the buccal temperature ranging around 36.6 C. The cutaneous temperature in a room kept at 22.2 C. and a humidity of 47 per cent was 25.2 C. at the base of the right great toe, which is at the lower range of normal encountered at the Peter Bent Brigham Hospital. The cutaneous temperature was studied before and after the immersion of both arms in a cold water bath at 15.5 C. for five minutes. There was a fall in the



Fig. 1.—A sharply demarcated wheal with borders corresponding to the edges of a piece of ice placed on the skin for five minutes. The wheal has the tough white appearance of pigskin and is surrounded by a fading reddish band. The smaller wheal over the left scapula (*A*) was produced by the intracutaneous injection of washings of physiologic solution of sodium chloride from the larger wheal. Just to the right of this is the hardly perceptible nonwhealed site (*B*) of the control injection of physiologic solution of sodium chloride.

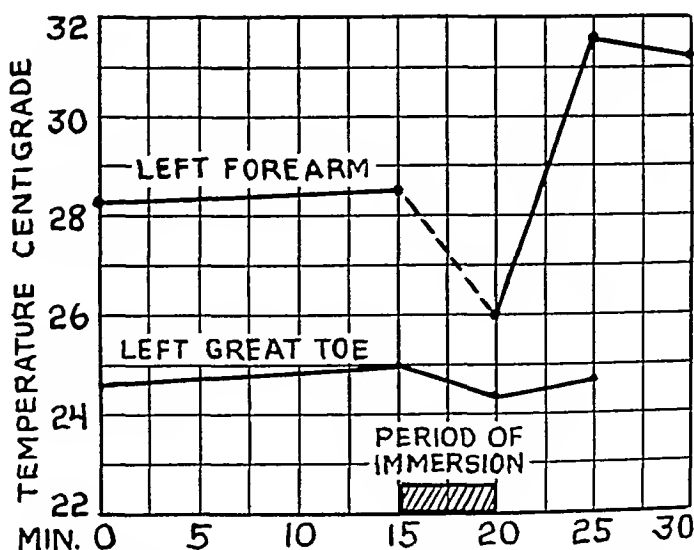


Fig. 2.—A graph indicating the primary fall in the temperature of the skin of the exposed arm with an exaggerated secondary rise in the local temperature. Corresponding but lesser changes took place in the corresponding foot.

cutaneous temperature during the period of immersion, followed by an exaggerated secondary rise. There were concomitant changes in the temperature of the lower extremities with primary fall and secondary less well marked rise. Figure 2 indicates the temperature of the skin of the left forearm and the left great toe before and after the period of immersion. A similar variation of temperature was observed in the right extremities.

Treatment.—Treatment consisted of repeated and increasing exposure to cold in the form of cold showers or rubbing the body with cakes of ice. As stated previously, the patient had already shown a certain degree of improvement when first seen, and it is impossible to state whether the further improvement shown was a natural and spontaneous development or the result of treatment. At the time of writing there is still mild sensitivity but the patient can tolerate from slight to moderate exposure to cold.

COMMENT

From the data obtained in the present case a brief can be held for no particular etiologic theory of urticaria due to cold. The failure to cause the formation of wheals by a local application of menthol which produces a sensation of cold and the failure to inhibit the reaction by a sufficient degree of anesthesia with procaine hydrochloride to make the skin insensitive to cold would seem to make the reaction independent of the nervous mechanism involved in the sensation of cold.

The occurrence of eosinophilia locally may not necessarily predicate an allergic reaction, for it has been shown that eosinophilia of the tissues can be produced just as readily by the intracutaneous injection of histamine as by substances causing an allergic reaction, such as pollens or emanations from animals.⁴⁰

As in the present case, Benjamin²⁷ reported a rise in the cutaneous temperature of his patient after the removal of the immersed arm from cold water. This was probably due to reactive hyperemia. Hewlett⁴¹ found an increased flow of blood to the arm during the reaction in a similar case in contrast to a diminished flow to the arm of a normal person similarly treated. Affolter²⁸ observed an increase in the oscillometric index indicating local vasodilatation.

The fact that no systemic reaction could be induced experimentally does not invalidate the humoral hypothesis, for possibly if a wheal were formed over a more extensive area the concentration of the hypothetical substances diffusing into the blood stream might have been adequate to cause general symptoms. It is conceivable that in the reactions produced a sufficient concentration of these substances diffuses into the intercellular spaces to be capable of transfer to a neighboring area of skin, but that the concentration attained in the blood stream is not

40. Kline, B. S.; Cohen, M. B., and Rudolph, J. A.: *Histologic Changes in Allergic and Nonallergic Wheals*, *J. Allergy* 3:531, 1932.

41. Hewlett, A. W.: *Active Hyperemia Following Local Exposure to Cold*, *Arch. Int. Med.* 11:507 (May) 1913.

enough to produce "shock" reactions or to be demonstrated by the Prausnitz-Küstner technic. It is possible that this criticism may be applied to many of the cases reported in the literature.

SUMMARY

A case of sensitivity to cold manifested in the development of local urticaria is described. The patient, a housewife 36 years old, who was nonsyphilitic, had the condition for one year. The entire cutaneous area and the buccal, pharyngeal and nasal mucosa were sensitive. There was no dermatographia or paroxysmal hemoglobinuria, and no hemolysin could be demonstrated in the blood. Tests for passive transfer were negative, and no systemic reaction followed local reaction experimentally produced. The formation of a wheal was not induced by the local application of menthol or inhibited by anesthesia with procaine hydrochloride. The temperature of the skin, ordinarily at the lower range of normal, showed a secondary rise following the local reaction. Improvement in the condition was either spontaneous or the result of specific desensitization. The etiology has not been determined.

EXPERIMENTAL CONCENTRIC AND ECCENTRIC CARDIAC HYPERTROPHY IN RATS

DAVID A. RYTAND, M.D.

AND

W. DOCK, M.D.

SAN FRANCISCO

Chanutin (with Ferris¹ and with Barksdale²) has recently shown that in rats deprived of 80 per cent of their renal tissue progressive renal lesions, arterial hypertension and cardiac hypertrophy develop. The width of the myocardial fibers of the right ventricle does not change, while the diameter of the fibers of the left ventricle bears "a substantial relationship" to the ratio of the weight of the heart to the surface area.

The comparison of a unidimensional or bidimensional method of measurement with a volumetric method has in the past led to serious misinterpretation of data. In this instance there has been no error in conclusions, but the comparison of width of the fibers (a linear measurement) with the weight of the heart (proportional to the total volume of all the fibers) has concealed an important fact, namely, that when the fibers of the heart of the rat hypertrophy in response to arterial hypertension they not only are thicker but are actually shorter than those of the normal rat (table 1).

This, we believe, is the first time that data conclusively proving the existence of concentric hypertrophy have been presented, and the fact seemed sufficiently important to justify further investigation, which has fully corroborated Chanutin's data.

METHODS

Renal insufficiency was produced in one group of rats, and the hypertrophied hearts were compared with the hearts of controls and with the hearts of rats fed desiccated thyroid.

From the Department of Medicine, Stanford University School of Medicine.

This study was aided by a grant from the Rockefeller Fluid Research Fund.

1. Chanutin, A., and Ferris, E. B.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: I. Control Diet, *Arch. Int. Med.* **49**:767 (May) 1932.

2. Chanutin, A., and Barksdale, E. E.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: II. Relationship of Left Ventricular Hypertrophy, the Width of the Cardiac Muscle Fiber and Hypertension in the Rat, *Arch. Int. Med.* **52**:739 (Nov.) 1933.

The rats were male albinos, 95 days of age at the beginning of the experiment. From the time of weaning and throughout the experiment they ate a stock diet containing 10 per cent casein and 18 per cent total protein. Full details of the strain of rats, environment, diet, basic methods and the like have been reported by MacKay and MacKay.³

Surface area was computed (without correction for gastro-intestinal content) by the formula $SA = 11.36 \times W^{\frac{2}{3}}$, in which W represents the body weight. The organs were weighed on Hartmann-Braun torsion balances, thus reducing errors of drying to a minimum.

When the animals were killed they were bled, with potassium oxalate as the anticoagulant; the cell volume and concentration of urea were determined on this blood.

TABLE 1.—*Changes in Length of the Fibers and in the Capacity of the Left Ventricle Calculated from the Weight of the Heart and Width of the Fiber **

Blood Pressure, Mm. Hg	Number of Rats	Heart Weight per 100 Sq. Cm.	Width of Fibers of the Left Ventricle	(A) Left Ventricle, Weight per 100 Sq. Cm.†	(B) Volume of Fibers per μ of Length‡	(C) Length of Fibers (Total) of Left Ventricle§	(D) Relative Capacity of Left Ventricle
120 or less	9	188 mg.	15 μ	134 Mg.	177 μ^3/μ	0.76 kilo-meters	100%
120 to 150	25	188 mg. $\pm 0\%$	16.6 μ $+11\%$	134 mg. $\pm 0\%$	217 μ^3/μ $+23\%$	0.62 kilo-meters -18%	85%
150 to 190	29	238 mg. $+26.5\%$	20.0 μ $+33\%$	134 mg. $+37\%$	314 μ^3/μ $+77\%$	0.59 kilo-meters -22%	105%
190 to 230	13	252 mg. $+34\%$	21.6 μ $+44\%$	198 mg. $+48\%$	365 μ^3/μ $+106\%$	0.54 kilo-meters -29%	103%

* The calculations are based on the data of Chanutin and Barksdale.² It is obvious that the increase in the volume of the fibers in the group with blood pressure over 190 is three times as great as the increase in the weight or volume of the heart and two and one-quarter times greater than the increase in the weight of the left ventricle. This involves a shortening of the length of the fibers at least 29 per cent, with no change in the capacity of the ventricle.

† This is calculated on the basis of no change in weight of the right ventricle and on a normal ratio of the weight of the left ventricle to that of the right of 2.47 : 1.

‡ Volume per unit of length equals the radius squared times π .

§ This is determined by dividing the figure in column A by that in column B.

|| The ventricular capacity is roughly proportional to the $3/2$ power of the inner surface area, and the surface area changes with the average width and length of the fibers lining it. The result is calculated by taking the $3/2$ power of the product of fiber width times fiber length, each in percentage of the control values.

Renal insufficiency was produced in seventeen rats by a modification of Chanutin's technic, which enabled determination of the amount of renal substance removed. The rat was anesthetized with ether, and the left kidney was delivered through a short incision below the costal margin. After decapsulation of the kidney, a bulldog clamp was applied to the renal pedicle for hemostasis, and the desired amount of tissue was removed at the poles, a ring forceps being used as a guillotine. An assistant weighed the removed tissue immediately. The amount of tissue to be removed was calculated from the surface area of the animal and the known average weight of the kidney of a rat. Thus the renal tissue could be reduced to any desired degree with some accuracy. The renal artery was

3. MacKay, L. L., and MacKay, E. M.: Factors Which Determine Renal Weight: I. Methods, *Am. J. Physiol.* **83**:179 (Dec.) 1927.

compressed for three minutes, within which time the required amount of tissue was removed. The clamp was then removed, and the kidney was allowed to return to its normal position. The amount of bleeding was small. The application of one catgut suture through the muscle layer and three or four skin clips completed the operation. Five days later the entire right kidney was removed and weighed. There was no attempt at asepsis in either operation.

In addition to the seventeen nephrectomized rats, sixteen male rats of the same age were set aside as controls, and to seven similar rats was fed desiccated thyroid, 0.1 per cent in the stock diet.

Seventy days after the second operation, when all the rats were 170 days of age, they were killed. After being weighed and anesthetized with ether, the rat was exsanguinated. The stump of the kidney (or both kidneys in the case of the controls and rats which had been fed thyroid) was removed and decapsulated. A sagittal incision was made; the surface was blotted on filter paper, and the kidney was weighed.

After the heart was removed, with the auricles and about 0.5 cm. of the great vessels, a blunt needle was introduced into the aorta and the left ventricle irrigated with a 0.9 per cent solution of sodium chloride. After the heart's contents had been expelled by pressure and the heart blotted on filter paper, the heart was weighed.

The heart was then moistened with saline solution and kept overnight at room temperature in a closely stoppered test tube. In from eighteen to twenty-four hours rigor mortis had disappeared. The heart was then removed from the tube; the aorta was cannulated and tied tightly about the glass cannula at the aortic ring and auriculoventricular groove. The left ventricle and cannula were filled with mercury, while the ventricle was manually compressed several times; the massage insured absence of rigor, and the alternate compression and expansion dislodged air and insured complete filling. The column of mercury was then raised to a constant marked height of 80 mm. above the aortic ring, and the entire preparation was weighed. The volume of the left ventricle was calculated by subtracting the weight of the fresh heart and the mercury-filled cannula and dividing by 13.6.

Finally, the ventricle was emptied of mercury, and the heart was fixed in Zenker's fluid and then placed in 80 per cent alcohol. The atria and great vessels were removed and weighed. The heart was divided into two portions along a plane perpendicular to and about the middle of a line from the base to the apex. The outer wall of the right ventricle was removed and weighed. The left ventricle (with the septum) was cleared of as much of the small amount of adherent mercury as possible and weighed. This crude weight of the wall of the right ventricle and of the left ventricle plus the septum was corrected to apportion the septum by means of a comparison of our method of ventricular separation with that of T. Lewis (similar to ours) and that of Herrmann.⁴ In view of their data, 30 per cent of the crude weight of the right ventricle was arbitrarily added to the observed value, and an equal amount was subtracted from the observed weight of the left ventricle and septum to give the corrected weights of the right and left ventricles.

The usual statistical methods were used in computing standard deviations and probable errors of the means.

4. Herrmann, G. R.: Experimental Heart Disease: I. Methods of Dividing Hearts, with Sectional and Proportional Weights and Ratios for Two Hundred Normal Dogs' Hearts, *Am. Heart J.* 1:213 (Dec.) 1925.

RESULTS

At the first operation the mean weight of the removed renal tissue was 102 mg. per hundred square centimeters, or 60 per cent of the mean weight of the single kidneys of the controls. The total removal of the right kidney five days later left the animal with 40 per cent of one kidney, or 20 per cent of the original total renal tissue (neglecting the five day hypertrophy of the stump).

Rats with this much kidney, though progressive polyuria and proteinuria developed and the values for blood urea were from 78 to 514 (mean 231) mg. per hundred cubic centimeters seventy days later, gained weight steadily (edema and ascites were not present) and could not be distinguished from the controls on inspection.

In table 2 are presented data showing the mean weight of the entire body, heart (fresh weight, capacity of the left ventricle and weight of the separated fixed chambers) and kidney for the control animals, those on which partial nephrectomy was carried out and those which were fed thyroid.

Weight of the Animals.—The difference in weight of the control and the partially nephrectomized animals was 12 ± 5.7 Gm., which was not significant statistically. The weight of the animals which were fed thyroid was 18 per cent below that of the controls.

Kidneys.—The weights are given as the total of both kidneys for the control animals and those fed thyroid. The kidneys of the latter group weighed 47 per cent more than those of the controls, an observation repeatedly reported.

The stump of the kidney had grown until its weight was 73 per cent of that of both normal kidneys, 145 per cent of that of one normal kidney and 370 per cent of that of the original stump.

Fresh Heart.—The average weight of the fresh heart of the partially nephrectomized animals was 30 ± 4.4 mg. per hundred square centimeters heavier than that of the controls, which was a significant increase (16 per cent). The weight of the heart of the rats fed thyroid had increased 54 per cent. Before computation of the weight of the fresh left ventricle the weight of the fresh total heart was reduced by an amount calculated by the relation of the weight of the fixed atria and great vessels to the weight of the fixed total heart. Computed on the basis of a normal ratio of the weight of the left ventricle to that of the right ventricle of 2:47:1 for the animals fed thyroid and no increase in the weight of the right ventricle in the nephrectomized rats, the respective weights of the fresh left ventricles were 158 per cent and 121 per cent of the control value.

The aortas of the group with renal insufficiency were grossly thickened and more rigid than those of the controls.

Fixed Heart.—For the control group the mean crude weight of the right ventricle was 28 ± 0.9 mg. per hundred square centimeters, and the group on which partial nephrectomy had been performed, 27 ± 1.1 . The difference was 1.0 ± 1.4 mg. For the control rats the mean crude weight of the left ventricle was 97 ± 1.9 mg. per hundred square centimeters; for the partially nephrectomized animals, 119 ± 2.5 mg. The difference was 22 ± 3.1 , which was a significant increase. The corrected ventricular weights are shown in table 2. It may be seen that in the partially nephrectomized animals hypertrophy was entirely confined to the left ventricle, while in the animals fed thyroid, cardiac hypertrophy involved both ventricles almost equally.

The ratio of the weight of the left ventricle to that of the right was almost the same in the controls and in the rats fed thyroid (2.47 and 2.73) but had increased to 3.20 in the animals on which partial nephrectomy was performed.

TABLE 2.—Mean Weight of the Kidneys and Heart and Mean Capacity of the Left Ventricle

Animals	Number of Rats	Weight at Death, Gm.	Surface Area at Death, Sq. Cm.	Weight of Fresh Heart, Mg. per 100 Sq. Cm.		Weight of Fixed Heart, Mg. per 100 Sq. Cm.			Capacity of Left Ventricle			
				Total	Calculated, Left Ventricle	Left to Right Ratio	Corrected, Left Ventricle	Corrected, Right Ventricle	Cubic Centimeters	Cubic Millimeters per 100 Sq. Cm.	Cubic Millimeters per 100 Mg. Fresh Heart	Cubic Millimeters per 100 Mg. Fresh Left Ventricle
Controls.....	16	274±3.6 100 %	479	189±1.5 100 %	129 100 %	2.47	89.0 100 %	36.0 100 %	0.311 100 %	71±2.2 100 %	37±1.0 100 %	55.2 100 %
Subjected to partial nephrectomy	17	262±4.4 96 %	463	219±1.1 116 %	156 121 %	3.20 1.3	110.9 125 %	31.7 86 %	0.317 102 %	75±1.8 106 %	35±1.1 95 %	48.1 87 %
Receiving thyroid..	7	225 82 %	420	291 151 %	291 138 %	2.71	142.0 160 %	52.0 144 %	0.337 163 %	133 187 %	46 124 %	65.0 118 %

The atria and great vessels averaged 5.6 mg. per hundred square centimeters in the control group, 9.7 mg. in the rats subjected to partial nephrectomy and 9 mg. in the animals fed thyroid.

Capacity of the Left Ventricle.—The similarity of capacity of the left ventricle in the control group and in the animals with partial nephrectomy (0.341 and 0.347 cc.) is in sharp contrast to the greatly dilated left ventricle of the animals fed thyroid (0.557 cc.). When computed on a basis of surface area the difference in capacities between the controls and the partially nephrectomized rats was $+4 \pm 2.8$ cu. mm. per hundred square centimeters; when computed on the basis of fresh heart weight, -2 ± 1.5 cu. mm. per hundred milligrams of heart. On each basis the rats fed thyroid had dilated left ventricles ($+87$ and $+24$ per cent). It may also be seen that the capacity per weight of the fresh left ventricle of the

TABLE 3.—*Changes in the Radius and Length of the Fibers Calculated from the Heart Weight and Capacity of the Left Ventricle**

Animals	Weight of Fresh Heart, Mg. per 100 Sq. Cm.	Weight of Fresh Left Ventricle, Mg. per 100 Sq. Cm.	Capacity of Left Ventricle, Cu. Mm. per 100 Sq. Cm.	(A) Inner Surface of Left Ventricle†	(B) Radius of Fibers of Left Ventricle‡	(C) Length of Fibers (Total) of Left Ventricle§
Control.....	189 100%	129 100%	71 100%	100%	100%	100%
Subjected to par- tial nephrectomy	219 116%	156 121%	75 106%	104%	116%	90%
Receiving thyroid..	291 154%	204 158%	133 187%	152%	104%	146%

* The calculations are based on the data reported in the paper. The close agreement of calculations based on our observations with those based on Chanutin's observations may be seen by comparing these data with those in table 1. Note the markedly different findings in the group that had been fed thyroid.

† This is calculated by taking the 2/3 power of the capacity of the left ventricle and expressing it as percentage of the control value.

‡ This is the quotient of $\frac{\text{left ventricular weight}}{\text{left ventricular inner surface}}$, each expressed as percentage of the control value.

§ This is determined by dividing the figure in column A by that in column B. (Since the ventricular weight varies as the product of the fiber length times the radius squared, and the inner surface of the ventricle varies as the fiber length times the radius, then $\frac{\text{weight}}{\text{surface}} = \text{radius}$, and $\frac{\text{surface}}{\text{radius}} = \text{length}$.)

animals with renal insufficiency actually diminished 13 per cent of that of the controls, while that of the rat fed thyroid increased 18 per cent.

In brief, the heart of the rat made hypertensive by deprivation of renal tissue reacts by an increase in the weight of its left ventricle alone, while the cavity of the left ventricle not only does not dilate but is relatively small in comparison to the weight of its surrounding myocardium. On the other hand, the heart of the rat fed thyroid becomes heavier in both ventricles equally, while the dilatation of the left ventricle closely parallels hypertrophy.

In table 1 calculations of the length of fibers and capacity of the left ventricle were made from Chanutin's data on the weight of the heart and the measured width of the fibers. In table 3 are shown

calculations of the width and length of fibers of the left ventricle based on the weight of the heart and measured capacity. The two sets of data are in close agreement and complement each other.

The data in table 3 again emphasize the distinction between the two mechanisms of hypertrophy; the myocardial fibers of the left ventricle of the rats fed thyroid were found to gain only 4 per cent in width but 46 per cent in length, while the fibers of the hypertensive rats were 16 per cent wider and 10 per cent shorter.

COMMENT

Many pathologists doubt and most physiologists deny the existence of cardiac hypertrophy without an increase in the capacity of the ventricles. In discussing this problem, some define concentric hypertrophy as an increase in weight with a decrease in the capacity of the chamber; others, as an increase in weight with unchanged capacity, and a few, as an increase in weight with relatively little increase in capacity. We use the term in the sense of increased weight without an increase in capacity, as distinguished from eccentric hypertrophy in which capacity as well as weight is increased. That is, in concentric hypertrophy there must be a decrease in the ratio of capacity to weight; in dilatation there is an increase in capacity without an increase in weight, and in eccentric hypertrophy the increase in weight and capacity are parallel, or there is a rise in the ratio of capacity to weight.

Concentric hypertrophy of a ventricle is an increase in the volume and weight of its myocardial fibers caused by an increase in the width of the fibers; it is associated with a relatively small ventricular cavity, no significant increase in capacity per unit of body surface area and a shortening of the total length of the fibers. Eccentric hypertrophy, on the other hand, implies a parallel increase in the volume of the cavity and in the wall of the ventricle, the latter mediated by lengthening of the myocardial fibers.

Disregarding definition, Krehl⁵ and Fishberg,⁶ with many clinicians, have accepted concentric hypertrophy as the usual course of events in a person with hypertension whose heart has not failed. Adami⁷ denied the existence of concentric hypertrophy on theoretical physiologic grounds and explained the reported instances as artefacts due to rigor

5. Krehl, L.: *The Principles of Clinical Pathology*, translated by A. W. Hewlett, ed. 2, Philadelphia, J. B. Lippincott Company, 1907, p. 60.

6. Fishberg, A. M.: *Hypertension and Nephritis*, ed. 2, Philadelphia, Lea & Febiger, 1931, p. 170.

7. Adami, J. G.: *Notes upon Cardiac Hypertrophy*, Montreal M. J. **23**:811 (May) 1895.

mortis. Kaufmann⁸ noted the condition rarely, and Mönckeberg⁹ photographed it. Dietlen¹⁰ urged that the term be dropped as the conception was in conflict with physiologic tenets and the condition impossible of existence.

There has been a striking absence of actual data concerning concentric hypertrophy. Two hundred years ago Stephen Hales¹¹ poured melted yellow wax into the left ventricles of animals and used the resulting values for volume and inner surface area of the ventricles in his computations on the work of the heart. Since then, there have apparently been only two workers who seriously studied ventricular volume in relation to hypertrophy.

Du Castel¹² measured the capacities of both ventricles in the hearts of 62 persons dying of various ailments and found in at least 1 instance *la véritable hypertrophie concentrique*. Widerøe¹³ investigated the weight and capacity of both ventricles in 311 cases; he reported his results and reviewed the literature on the size of the heart in an extensive monograph. On the average, in 9 cases of chronic nephritis the ratio of the weight of the left ventricle to the body weight increased 100 per cent above that of the controls; the ratio of the weight of the right ventricle to the body weight increased 57 per cent, and the ratio of the capacity of the left ventricle to that of the right ventricle increased 51 per cent. The data of both authors are complicated by the heterogeneity of their series and by the necessity of including cases of heart failure, so that the bearing of the data on the existence of concentric hypertrophy is questionable. By the use of experimental animals killed at will and with different methods of obtaining data, both Chanutin and we have shown that when there is renal insufficiency the heart of a rat reacts to hypertension with unquestionable concentric hypertrophy of the left ventricle.

8. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 1, p. 73.

9. Mönckeberg, J. G.: Die Erkrankungen des Myokards und des spezifischen Muskelsystems, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 350.

10. Dietlen, Hans: Herzgrösse, Herzmessmethoden; Anpassung, Hypertrophie, Dilatation, Tonus des Herzens, in Bethe, A.; Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol. 7, p. 351.

11. Hales, Stephen: Statical Essays, London, W. Innys and others, 1733.

12. du Castel: Recherches sur l'hypertrophie et la dilatation des ventricules du cœur, Arch. gén. de méd. **145**:25, 1880.

13. Widerøe, Sofus: Die Massenverhältnisse des Herzens unter pathologischen Zuständen, Christiania, Jacob Dybwad, 1911.

Current physiologic teaching¹⁴ holds that the heart responds to demands for added work by dilatation (lengthening of the fibers), for, according to Starling's "law of the heart," the energy of contraction is a function of the length of the muscle fibers. If the demand for increased work continues the dilated heart becomes hypertrophied (the stretched fibers increase in width). It has been largely on the authority of Starling's law that the existence of concentric hypertrophy has been denied.

However, an important point in cardiodynamics first raised by Paterson and Starling and amplified by Gesell has been neglected. The former authors¹⁵ stated:

If the cavity of each ventricle were perfectly spherical the tension on each muscle fiber would be greater the greater the capacity of the sphere, assuming the intracardiac pressure to remain constant. (The total pressure on the whole of the boundary layer of a sphere will vary as its surface and therefore as the square of the radius. While the length of each muscle fiber lying in the circumference of the sphere would vary directly as the radius, the amount of fluid to be forced out by a given shortening of the muscle fibers would vary as the cube of the radius.) Since under normal conditions the capacity of the heart cavities becomes less during the contraction of the ventricle, a constant tension on the muscle fibers would tend to produce a pressure in the heart cavities which would increase steadily as the emptying proceeded and their capacity became smaller. . . . It may be remembered that . . . most skeletal muscles contract in this way, since they act at a greater mechanical advantage . . . when contracted than when commencing their contraction.

Gesell¹⁶ made an extensive mathematical study of the surface-volume relation and showed that "the efficiency of the contractile energy increases more rapidly per unit of muscle shortening the smaller the initial volume, a factor which would point to an optimum initial volume for maximum utilization of contractile energy."

In a ventricle with constant contractile energy a given unit of shortening of the muscle fibers will expel a comparatively large volume (at relatively low pressure) if the initial capacity is great, while the same amount of shortening will develop a greater endocardiac pressure the smaller the initial capacity (with a smaller stroke output). Viewed in this light, the contrasting mechanisms of hypertrophy exhibited by the heart of the rat with hypertension (concentric) and that of the rat with hyperthyroidism (eccentric) are readily understood.

14. Starling, E. H.: *Principles of Human Physiology*, ed. 6, revised by C. L. Evans, Philadelphia, Lea & Febiger, 1933, p. 773.

15. Patterson, S. W., and Starling, E. H.: On the Mechanical Factors Which Determine the Output of the Ventricles, *J. Physiol.* **48**:357 (Sept. 8) 1914.

16. Gesell, Robert A.: Cardiodynamics in Heart Block as Affected by Auricular Systole, Auricular Fibrillation and Stimulation of the Vagus Nerve, *Am. J. Physiol.* **40**:267 (April 1) 1916.

The optimal initial size of the heart of a subject with hyperthyroidism, which must expel an increased minute output against presumably normal peripheral resistance, should obviously be greater (in both chambers) than that of the heart of a subject with hypertension, which must expel a normal minute output against an increased peripheral resistance in the systemic circuit. As a matter of fact, the heart of a subject with hyperthyroidism does present parallel increases in myocardial weight and ventricular capacities, while the fibers of the left ventricle of the heart of the hypertensive subject grow wider and shorter. When hypertension develops gradually it is unlikely that dilatation of the heart occurs at any time; hypertrophy in such cases at least is not preceded by lengthening of the fibers. We have, however, no actual data on the diastolic volume in vivo.

CONCLUSIONS

1. The heart of the rat reacts to the arterial hypertension of renal insufficiency by the production of concentric hypertrophy of the left ventricle.
2. In concentric hypertrophy so induced, the myocardial fibers of the left ventricle are increased in width and decreased in length.
3. The heart of the rat reacts to artificial hyperthyroidism by the production of eccentric hypertrophy involving the two ventricles equally.
4. In eccentric hypertrophy so induced, the myocardial fibers do not show a significant change in width but lengthen greatly.
5. A consideration of cardiodynamics shows that concentric hypertrophy is the optimum compensatory mechanism for the heart of the subject with hypertension and eccentric hypertrophy for the heart of the subject with hyperthyroidism.

SUMMARY

With a modification of Chanutin's technic for bringing about renal insufficiency, cardiac hypertrophy was produced in a group of albino rats; the hearts were compared with normal hearts and with hearts with hypertrophy induced by the feeding of thyroid. Our results were shown to confirm and extend those of Chanutin. The findings were discussed in relation to cardiodynamic principles.

STUDIES OF HEPATIC FUNCTION

II. IN PORTAL CIRRHOSIS AND CONGESTIVE HEART FAILURE

A. CANTAROW, M.D.

PHILADELPHIA

No one can gainsay the inadequacy, in many respects, of present-day methods of investigating the functional efficiency of the liver. General recognition of this fact apparently has led to the feeling among many clinicians that little information can be obtained by these methods. As a result, little or no attempt is made to determine the state of hepatic function in many clinics in which elaborate studies of renal function, for example, may be a matter of routine. My experience in this field has convinced me of the value of a careful and detailed study of hepatic function by readily available methods in a great variety of clinical disorders, and it has led to the belief that much of the discredit which is attached to these procedures is due to errors of interpretation rather than to faults inherent in the methods.

The present report consists of observations made on patients with portal cirrhosis, Banti's disease and congestive heart failure. The bilirubin content of the serum was determined by the quantitative van den Bergh method as modified by Thannhauser and Andersen. As stated in a previous report,¹ the normal range of serum bilirubin, in my experience, is from 0.1 to 1.0 mg. per hundred cubic centimeters, the value in 50 per cent of cases falling below 0.5 mg. per hundred cubic centimeters and in 95 per cent, below 0.8 mg. Bromsulphalein was injected in a dosage of 2 mg. per kilogram, and a single determination was made at the end of thirty minutes. The cholesterol content of the plasma was determined by the method of Myers and Wardell as modified by Oser and Karr,² and the amount of urobilinogen in the urine, by the method of Wallace and Diamond.³

PORTAL CIRRHOSIS

There were twenty-two patients with portal cirrhosis. The detailed data are presented in table 1. It will be noted that normal findings were

From the Laboratory of Biochemistry and the Department of Medicine, Jefferson Hospital.

1. Cantarow, A.: Studies of Hepatic Function: I. Noncalculous and Calculous Cholecystitis, *Arch. Int. Med.* **54**:540 (Oct.) 1934.

2. Oser, B., and Karr, W. G.: The Lipoid Partition in Blood in Health and in Disease, *Arch. Int. Med.* **36**:507 (Oct.) 1925.

3. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, *Arch. Int. Med.* **35**:698 (June) 1925.

obtained in only four (18.1 per cent) cases in this series. Visible jaundice was present in eight instances (cases 1 [not on admission], 2, 5, 6, 7, 9, 12 and 15), although hyperbilirubinemia was present in three others and also in case 1 at the time of admission. Of the seven normal values for serum bilirubin, three were between 0.9 and 1 mg., figures which would be obtained in less than 5 per cent of normal persons. This observation in itself indicates the importance of the routine determination of the serum bilirubin concentration in cases of suspected hepatic dysfunction and the unreliability of clinical observa-

TABLE 1.—*Data on Cases of Portal Cirrhosis*

Case	Date	Direct Van den Bergh Reaction	Serum Bilirubin, Mg. per 100 Cc.	Brom- sulphalein Retention, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Uro- bilinogen in the Urine	Ascites
1	6/ 3/32	0	1.2	0	...	1:20	..
	6/19/32	+	2.4	0	0
	10/ 5/32	+	3.0	20	100
	11/16/32	+	6.4	20
2	+	3.8	0	...	1:20	+
3	0	1.1	10	0
4	11/23/32	0	1.2	40	164	1:300	..
	12/ 8/32	0	1.6	60	0
5	+	6.0	40	162	+
6	+	3.7	40	200	1:200	+
7	+	2.4	40	+
8	0	0.4	10	0
9	+	4.0	80	131	1:20	+
10	1/ 3/33	0	0.92	25	119
	1/26/33	0	0.92	60	0
11	0	1.0	5	131	1:10	0
12	+	2.43	55	158	1:50	0
13	0	0.48	10	100	1:40	0
14	0	1.0	40	211	1:200	0
15	+	8.2	35	...	1:400	+
16	0	0.63	10	186	1:100	0
17	+	1.5	25	0
18	0	0.55	10	...	1:50	0
4 cases.....			0.34-0.91	0	126-164	1:10-1:40	0

tion in the detection of early or latent jaundice, a fact which is generally recognized.

Rolleston and McNee⁴ stated that jaundice is not a prominent feature of portal cirrhosis but that it occurs in more than one third of the cases at some time during the course of the disease. They reported that jaundice was present in 36.5 per cent of a collected series of 293 cases. It has been found⁵ to be present in only 8 per cent of

4. Rolleston, H. D., and McNee, J. W.: *Diseases of the Liver, Gall Bladder and Bile Ducts*, ed. 3, New York, The Macmillan Company, 1929, p. 258.

5. *Diseases of Metabolism and of the Digestive Tract*, Vienna letter, J. A. M. A. 85:1573 (Nov. 14) 1925.

ninety cases of portal cirrhosis. Nissen⁶ noted icterus in sixty-two of seventy-seven cases post mortem, when pigmentation of the skin is more evident than during life, and Chapman, Snell and Rowntree⁷ reported its presence in forty-three (38.4 per cent) of 112 cases of the late stages of the disease. All are agreed that jaundice is usually absent in the preascitic stage, although slight grades of hyperbilirubinemia have been observed during this period by Diamond,⁸ by Gilbert, Herscher and Posternack⁹ and by Greene, McVicar, Snell and Rowntree.¹⁰ In the present series, ascites was demonstrable in cases 2, 5, 6, 7, 9 and 15, with serum bilirubin values ranging from 2.4 to 8.2 mg. per hundred cubic centimeters. No ascites was present (at autopsy) in case 1, in which the serum bilirubin concentration was 6.4 mg. However, there seems little question that in the absence of such complicating factors as cholangitis, cholelithiasis and duodenitis the higher values are obtained in the more advanced stages of the cirrhotic process. It is of interest to note in this connection, however, that ascites may in some instances be in part dependent on factors other than cirrhosis, e. g., chronic peritonitis or perihepatitis, and may not indicate accurately the severity of the cirrhotic process. For example, of the seventy-seven patients studied at autopsy by Nissen,⁶ forty-four presented both jaundice and ascites, eighteen jaundice without ascites and fifteen ascites without jaundice. It is evident that whereas in the experience of the majority of observers ascites usually precedes the development of visible icterus, this is not invariably the case, and varying degrees of hyperbilirubinemia may be present in many cases before ascites can be demonstrated.

The direct van den Bergh reaction was positive in every instance in this series in which the serum bilirubin was above 2 mg. per hundred cubic centimeters and was negative in every case in which the value was below this figure, with one exception (case 17, 1.5 mg.). A positive direct reaction in portal cirrhosis may be due to extensive hepatic necrosis or to intrahepatic canalicular or extrahepatic ductal obstruction. As pointed out by Althausen,¹¹ the newly formed hyperplastic nodules

6. Nissen, H. A.: *Cirrhosis of the Liver Showing Jaundice and Ascites*, M. Clin. North America **4**:555, 1920.

7. Chapman, C. B.; Snell, A. M., and Rowntree, L. G.: *Decompensated Portal Cirrhosis*, J. A. M. A. **97**:237 (July 25) 1931.

8. Diamond, J. S.: *The Value of Routine Estimations of Blood Bilirubin*, Am. J. M. Sc. **176**:321, 1928.

9. Gilbert, A.; Herscher, M., and Posternack, S.: *Sur la signification de l'anneau bleu produit par le réactif de Gmelin dans certains sérums*, Compt. rend. Soc. de biol. **55**:584, 1903.

10. Greene, C. H.; McVicar, C. S.; Snell, A. M., and Rowntree, L. G.: *Diseases of the Liver: VI. A Comparative Study of Certain Tests for Hepatic Function in Cases of Cirrhosis of the Liver*, Arch. Int. Med. **40**:159 (Aug.) 1927.

11. Althausen, T. L.: *Functional Aspects of Regenerated Hepatic Tissue*, Arch. Int. Med. **48**:667 (Oct.) 1931.

frequently lack connection with bile channels, which may account in part for the development of a regurgitation (Rich) type of hyperbilirubinemia in the later stages of the disease. A positive direct reaction has been reported in patients with portal cirrhosis by Greene, McVicar, Snell and Rowntree,¹⁰ by Cabot,¹² by Comfort and Snell,¹³ by Barker¹⁴ and by Shattuck, Browne and Preston.¹⁵ A positive direct reaction was obtained by Barker¹⁴ with a serum bilirubin concentration as low as 1 mg. per hundred cubic centimeters, and, on the other hand, Comfort and Snell¹³ reported a negative direct reaction in one case with a serum bilirubin concentration of 3.3 mg. per hundred cubic centimeters.

Some degree of retention of bromsulphalein was present in seventeen (77.3 per cent) of the twenty-two cases in this series, although no retention was noted in case 1 at the time of admission. Cases 1 and 2 are only instances, in the present series, of hyperbilirubinemia without retention of dye, whereas the reverse, retention of dye (from 5 to 60 per cent) without hyperbilirubinemia, was noted in seven cases (cases 8, 10, 11, 13, 14, 16 and 18). It is evident that bromsulphalein retention can be demonstrated frequently in early stages of portal cirrhosis before hyperbilirubinemia has developed. Some degree of dye retention was noted in eighty of eighty-seven cases reported by Chapman, Snell and Rowntree.⁷ Other reports are as follows: Cabot,¹² from 45 to 70 per cent; Barker,¹⁴ slight retention; Eusterman,¹⁶ slight retention; Piersol and Rothman,¹⁷ from 0 to 20 per cent; Epstein,¹⁸ from 0 to 25 per cent; O'Leary, Greene and Rowntree,¹⁹ from 2 to 40 per cent; Robertson, Swalm and Konzelmann,²⁰ from 2 to 30 per cent; Foley,²¹

12. Cabot, R. C.: Case Records of the Massachusetts General Hospital, New England J. Med. **205**:107, 222 and 1056, 1931.

13. Comfort, M. W., and Snell, A. M.: Treatment of Portal Cirrhosis, M. Clin. North America **15**:107, 1931.

14. Barker, L. F.: Presentation of Cases of Portal Cirrhosis, M. Clin. North America **14**:87 and 99, 1930.

15. Shattuck, H. F.; Browne, J. C., and Preston, M.: Clinical Value of Some Recent Tests for Liver Function, Am. J. M. Sc. **170**:510, 1925.

16. Eusterman, G. B.: Errors in the Diagnosis of Diseases Associated with Jaundice, Ann. Int. Med. **6**:608, 1932.

17. Piersol, G. M., and Rothman, M. M.: Practical Value of Liver Function Tests, J. A. M. A. **91**:1768 (Dec. 8) 1928.

18. Epstein, E. Z.: The Cholesterol Partition of the Blood Plasma in Parenchymatous Diseases of the Liver, Arch. Int. Med. **47**:82 (Jan.) 1931.

19. O'Leary, P. A.; Greene, C. H., and Rowntree, L. G.: Diseases of the Liver: VIII. The Various Types of Syphilis of the Liver with Reference to Tests for Hepatic Function, Arch. Int. Med. **44**:155 (Aug.) 1929.

20. Robertson, W. E.; Swalm, W. A., and Konzelmann, F. W.: Functional Capacity of the Liver: Comparative Merits of the Five Most Popular Tests, J. A. M. A. **99**:2071 (Dec. 17) 1932.

21. Foley, E. F.: The Clinical Value of Tests of Liver Function, Arch. Int. Med. **45**:302 (Feb.) 1930.

from 5 to 30 per cent; Shattuck, Browne and Preston,¹⁵ from 0 to 16 per cent. Greene, McVicar, Snell and Rowntree¹⁰ found retention of from 0 to 35 per cent in patients with ascites and a contracted liver, from 5 to 28 per cent in those with ascites and an enlarged liver and from 0 to 11 per cent in those without ascites. In the present series it is apparent that the relationship between the degree of retention of dye and the presence of ascites is not nearly as consistent as is the relation of the latter to the degree of hyperbilirubinemia.

As was noted in previously reported studies of hepatic function in cases of cholecystitis,²² the absence of a consistent correlation between the degree of retention of bromsulphalein and the concentration of serum bilirubin is of distinct practical value as well as of theoretical significance in evaluating the relative significance of obstructive and nonobstructive factors in the mechanism of production of the existing disturbance of hepatic excretory function. Although the higher grades of retention of dye are frequently found to be associated with the higher levels of bilirubinemia, this relationship is by no means invariable in portal cirrhosis. For example, in case 1, the retention of dye remained at 20 per cent while the concentration of serum bilirubin rose from 3 to 6.4 mg. per hundred cubic centimeters; in case 2 there was no retention of dye with a serum bilirubin concentration of 3.8 mg. per hundred cubic centimeters. Cases 8, 10, 13, 16 and 18 also illustrate the dissociation of these two phases of the excretory function of the liver. Such findings are not obtained in conditions in which an obstructive mechanism is operative, except during periods following relief of obstruction, such as after passage or removal of a stone from the common bile duct.

There is considerable difference of opinion regarding the pathogenesis of hyperbilirubinemia in portal cirrhosis. Rich²³ placed this condition in the category of "regurgitation" jaundice, due to necrosis of hepatic cells, which occurs in the late stages of the disease. Other observers attribute this phenomenon to radicular cholangitis, to cholangitis of the larger ducts, to duodenitis and even to compression and kinking of the extrahepatic ducts. As mentioned before, Althausen¹¹ stated the belief that the regurgitation type of hyperbilirubinemia in the later stages may be due to the fact that the newly formed hyperplastic nodules frequently lack connection with bile channels. In view of the frequent occurrence of dissociation of the bilirubin concentration and the retention of bromsulphalein, it appears likely that primary impair-

22. Cantarow, A.: The van den Bergh Reaction and the Bromsulphalein Test in the Estimation of Hepatic Functional Impairment, *Am. J. M. Sc.* **184**:228, 1932; footnote 1.

23. Rich, A. R.: The Pathogenesis of Jaundice, *Bull. Johns Hopkins Hosp.* **47**:338, 1930.

ment of the function of the hepatic cells plays a much more important part than any obstructive mechanism in the production of hyperbilirubinemia in portal cirrhosis. The presence of excessive urobilinuria in many cases and the occasionally subnormal concentration of plasma cholesterol (cases 1, 9, 10, 11 and 13) add further support to this view.

BANTI'S DISEASE

Observations made on four patients with splenic anemia in whose cases the diagnosis of Banti's disease was made are presented in table 2. Advanced hepatic involvement, with ascites, was present in cases 2 and 3. What has been said regarding the findings in portal cirrhosis applies equally here. It may be noted that in case 4 a negative direct van den Bergh reaction and normal excretion of bromsulphalein were present in association with a serum bilirubin concentration of 2.7 mg. per hundred cubic centimeters.

TABLE 2.—*Data on Cases of Banti's Disease*

Case	Date	Direct Van den Bergh Reaction	Serum Bilirubin, Mg. per 100 Cc.	Brom- sulphalein Retention, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Urobilinogen in the Urine
1	+	1.5	20	...	1:60
2	+	6.0	60	162	1:100
3	+	3.6	30	...	1:200
4	6/27/33	0	2.7	0	147	1:100
Spleneectomy	7/15/33	0	1.5	0
	7/15/33	0	0.8	1.20
	9/20/33	0				

CONGESTIVE HEART FAILURE

Data were obtained in forty-two cases of congestive heart failure of varying degree. These are presented in detail in table 3. Abnormal findings were obtained in fourteen cases (33 per cent). No attempt is made to classify these according to the nature of the underlying lesions and of the degree of pulmonary and hepatic involvement, obviously factors of great importance in this connection.

Visible jaundice was noted in only two patients (cases 7 and 12), although some degree of hyperbilirubinemia was present in eight additional patients. In view of the significance of this phenomenon in patients with congestive heart failure, this observation emphasizes the importance of the determination of the serum bilirubin concentration and the unreliability of the clinical recognition of jaundice of relatively mild degree. As pointed out by Fishberg,²⁴ a state of latent or mild icterus in such patients is frequently masked by cyanosis. Foley²¹

24. Fishberg, A. M.: Jaundice in Myocardial Insufficiency, *J. A. M. A.* **80**: 1516 (May 26) 1923.

reported serum bilirubin values ranging from 0.4 to 7.7 mg. per hundred cubic centimeters in a group of thirty patients with chronic passive congestion of the liver, visible jaundice being noted in eleven. Andrewes²⁵ obtained values ranging from 0.4 to 7.5 van den Bergh units (0.16 to 3 mg. per hundred cubic centimeters) in fourteen patients with cardiac disease. He stated that patients without gross failure all gave a normal result while those with gross failure, especially with enlarged livers, usually had latent if not obvious jaundice; hepatic enlargement and hyperbilirubinemia did not always go hand in hand. Kugel and Lichtman,²⁶ in a study of fifteen cases of "cardiac" jaundice, reported values for serum bilirubin ranging from 0.5 to 8 mg. per

TABLE 3.—*Data on Cases of Congestive Heart Failure*

Case	Date	Direct Van den Bergh Reaction	Serum Bilirubin, Mg. per 100 Cc.	Brom- sulphalein Retention, per Cent	Plasma Cholesterol, Mg. per 100 Cc.	Uro- bilinogen in the Urine	Edema
1	6/ 1/32	0	0.76	5
	7/14/32	0	1.48	40	...	1:40	+++
2	+	1.5	10	+
3	0	1.25	15	212	+
4	0	0.37	5	+
5	+	1.5	40	188	1:10	++
6	0	0.7	10	+
7	+	4.1	30	118	1:60	+++
8	0	1.0	10	++
9	11/10/32	0	1.89	25	++
	12/ 2/32	0	1.2	0	+
10	11/21/32	0	1.68	60	++
	11/25/32	0	1.8	40
	12/ 5/32	0	0.84	40	...	1:30	++
11	+	2.6	20	164	+
12	+	3.0	100	...	1:40	++
13	0	1.2	10	+
14	0	0.63	100	172	+++
28 cases.....			0.12-0.94	0	126-206	0-1:20	+ to +++

hundred cubic centimeters, the content being above 2 mg. in twelve instances. A prompt direct van den Bergh reaction was obtained in ten of eleven cases in which this test was performed. This reaction was obtained in only five of the ten patients with hyperbilirubinemia in the present series. In Jolliffe's²⁷ series of sixteen patients, not all of whom were visibly jaundiced, 93 per cent showed some laboratory evidence of impaired function of the liver although in only one instance were the results of all tests employed abnormal.

25. Andrewes, C. H.: A Clinical Study of van den Bergh's Test in Jaundice, *Quart. J. Med.* **18**:19, 1924.

26. Kugel, M. A., and Lichtman, S. S.: Factors Causing Clinical Jaundice in Heart Disease, *Arch. Int. Med.* **52**:16 (July) 1933.

27. Jolliffe, N.: Liver Function in Congestive Heart Failure, *J. Clin. Investigation* **8**:419, 1930.

There is no unanimity of opinion regarding the pathogenesis of hyperbilirubinemia in patients with congestive heart failure. The two major opposing concepts stress the fundamental importance, respectively, of (1) hepatic functional impairment and (2) formation of excess bilirubin from hemoglobin liberated from areas of pulmonary infarction. Fishberg²⁴ explained the development of jaundice on the basis of two factors: (1) increased destruction of stagnated red blood cells by cells of the reticulo-endothelial system (liver, lungs, spleen); (2) impaired excretion of bilirubin by the liver as a result of injury of hepatic cells incident to chronic passive congestion. Rich,²³ Rosin,²⁸ Campbell²⁹ and others demonstrated the effect of anoxemia in producing atrophy of cells about the efferent veins of the hepatic lobules, and Rich and most subsequent observers have expressed the belief that this factor is the basis of the characteristic changes in the hepatic cells present in cases of myocardial failure. Rich,²³ however, stated the belief that jaundice does not occur in the presence of anoxemia unless there is a simultaneous overproduction of bilirubin. According to Barron,³⁰ in the great majority of instances this form of hyperbilirubinemia is of the retention type, with a negative direct van den Bergh reaction; aggravation of the existing state of anoxemia by the development of pulmonary infarction, as shown by Binger, Brow and Branch,³¹ may convert latent into visible jaundice. As the condition progresses and damage to the hepatic cells increases, actual necrosis may occur, "regurgitation" jaundice develop and a positive direct van den Bergh reaction be obtained.

Kugel and Lichtman²⁶ expressed an inclination toward the opposite view on the basis of their clinical and morphologic study of a rather large series of bases. Their concept is as follows: Bilirubin is formed from hemoglobin liberated from areas of pulmonary infarction and is absorbed into the circulation. The excretory capacity of the liver is impaired because of anoxemia and, in some cases, infection. However, unless extensive hepatic disease is present, i. e., true cirrhosis, the jaundice is primarily pulmonogenic, the deleterious effects of anoxemia being of secondary importance.

The data reported here throw no light on this problem. It is of interest, however, to note again the absence of correlation between the degree of retention of bromsulphalein and that of bilirubinemia in several instances. The severity of the condition of myocardial failure

28. Rosin, A.: *Morphologische Organveränderungen beim Leben unter Luftverdünnung*, Beitr. z. path. Anat. u. z. allg. Path. **80**:622, 1928.

29. Campbell, J. A.: Concerning the Problem of Mount Everest, *Lancet* **2**:84, 1928.

30. Barron, E. S. G.: Bilirubinemia, *Medicine* **10**:77, 1931.

31. Binger, C. A.; Brow, G. R., and Branch, A.: Experimental Studies on Rapid Breathing: I and II, *J. Clin. Investigation* **1**:127 and 155, 1924.

appeared to be more consistently related to the degree of retention of dye than to the concentration of serum bilirubin (e. g., cases 10 and 14) in the cases in which abnormal findings were obtained. These observations suggest that hepatic functional impairment, as indicated by retention of dye, is present in practically all cases with hyperbilirubinemia but that marked impairment of excretion of dye may be present without hyperbilirubinemia. Whether the latter observation may be interpreted as evidence that jaundice in cases of congestive heart failure is not primarily dependent on hepatic functional impairment is a question which cannot be answered until more is known regarding the exact method and path of excretion of bromsulphalein by the liver and what relation it bears to the excretion of bilirubin.

SUMMARY

Hyperbilirubinemia or abnormal retention of bromsulphalein or both were present in seventeen of twenty-two patients with portal cirrhosis. Visible jaundice was present in eight of twelve patients with hyperbilirubinemia.

Although ascites usually precedes the development of visible icterus, varying degrees of hyperbilirubinemia may be present in many cases before ascites can be demonstrated.

Retention of bromsulphalein was noted in 77.3 per cent of the cases in this series, being at times exhibited by patients with normal serum bilirubin values (seven cases). The relationship between retention of dye and the presence of ascites was not as consistent as was the relation of the latter to the degree of hyperbilirubinemia.

This dissociation of the retention of dye and that of bilirubin is practically never encountered in obstructive types of hyperbilirubinemia and suggests that primary impairment of the function of the hepatic cells is of fundamental importance in the production of hyperbilirubinemia in cases of portal cirrhosis. Similar observations were made in four cases of splenic anemia (Banti's disease).

Hyperbilirubinemia was present in ten of forty-two cases of congestive heart failure, in only two of which there was visible jaundice. Abnormal retention of bromsulphalein was present in fourteen cases. The severity of the condition appeared to be more consistently related to the degree of retention of dye than to the concentration of serum bilirubin.

Marked impairment of excretion of dye may occur in the absence of hyperbilirubinemia. Although not conclusive, this observation suggests that some factor, probably pulmonary infarction, other than hepatic functional impairment is necessary for the production of hyperbilirubinemia in patients with congestive heart failure.

Progress in Internal Medicine

PERIPHERAL VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE WITH A
CRITICAL REVIEW OF SURGICAL TREATMENT

GEORGE W. SCUPHAM, M.D.

Assistant Professor of Medicine, Northwestern University; Assistant Attending
Physician, St. Luke's Hospital, and Attending Physician, Cook County Hospital

AND

GÉZA DE TAKÁTS, M.D.

Associate Professor of Surgery, University of Illinois, College of Medicine, and
Associate Attending Surgeon, St. Luke's Hospital

CHICAGO

A REVIEW OF SOME OF THE RECENT LITERATURE
By DR. SCUPHAM

The advances which have been made both in the understanding of the diseases of the blood vessels of the extremities and in their treatment are an example of what can be accomplished when interest is widely aroused in a particular subject.

This interest not only has resulted in increased information concerning the diseases in question but has given rise to increased knowledge of the physiology of the autonomic nervous system and its relation to the circulation, as well as of the function, normal and abnormal, of so important a group of vessels as the capillaries. Earlier observations have been subjected to critical analysis with clarification of the concepts. Just as all diseases of the blood vessels were at one time included under the term arteriosclerosis and the inflammatory and spasmodic varieties, embolism and thrombosis, split off, so further clarification of the present classifications is being sought. The problems are by no means solved, but important advances have been made.

The diagnosis of vascular disease is now being made in a relatively early stage, whereas only a short time ago such a condition continued almost invariably to gangrene and amputation of the extremity at a high level or loss of life. The advances in treatment have been as important as the progress in the means of diagnosis.

Not only in diseases of the arteries of the extremities has the better understanding of the physiopathologic processes involving the

blood vessels become apparent, but recent studies on these vessels have given increased insight into some of the more obscure types of visceral vascular diseases.

The initial advances were the result of detailed observation and study of individual cases; the later one represented the development of new methods and apparatus as well as the application of physiologic experiments to the study of the circulation.

Riesman¹ has recently commented on the rapid development of interest in the study of vascular diseases to the point of specialization. This enthusiasm has advanced the knowledge, but the danger of limitation to too narrow a field is obvious. Vascular diseases must be approached from the standpoint of medicine as a whole. They cannot be limited to any field, as the problems are pertinent to all branches.

This review is by no means inclusive of all the publications on the subject, nor is the bibliography complete. In the attempt to make the subject somewhat less confusing than it might otherwise be, the study has been extended back for five years or more, and certain papers have been selected because they are representative of a special type of work or include or confirm the reports of others on the same subject. In order to keep within the limitations of space, the same procedure has been applied to the more recent contributions.

THE CAPILLARY CIRCULATION

There has been much variation of opinion in regard to both the structure of the capillaries and their reactions. This disagreement is the result, in part at least, of interpretations based on observations on specimens preserved by fixation or injection, and the minute and delicate structure of these vessels may be much altered from their normal character in living persons. The many careful studies on living amphibians and mammals have resulted in a great increase in the knowledge, but the variations which occur in different species as well as in different structures of the same animal make the application of these observations to man uncertain.

Newer methods for the study of the living capillaries in man have begun to clarify the knowledge previously gained and have made distinct additions to it. The application of photography² to the observation of the vessels in the nail fold by means of the capillary microscope is now a satisfactory procedure for obtaining permanent records for comparison.

1. Riesman, David: Vascular Crises, *Ann. Int. Med.* **8**:1047 (March) 1935.

2. Duryee, A. W., and Wright, I. S.: Present Day Technique for the Study of Human Capillaries, *Am. J. M. Sc.* **185**:664 (May) 1933.

The wall of a capillary³ consists of an inner endothelial layer and an apparent outer muscular layer. This muscular layer is not continuous but consists of a network of fine fibrils which connect with the Rouget cells. These cells and fibrils make up the contractile system of the capillaries. The presence of these cells in man has been questioned, but Wright is of the opinion that Rouget cells or their counterpart exist.

Kuntz⁴ states:

That the capillary vessels are functionally innervated is quite generally conceded both by reason of observed anatomical relationship of nerve fibers to the capillaries and by reason of the physiological behavior of the capillaries under normal and experimental conditions. The data available at present, however, do not warrant the conclusion that all capillaries are directly innervated.

Krogh⁵ is of the opinion that if the existence of Rouget cells constituting a muscular coat is accepted, innervation by the sympathetic nervous system is to be expected. This he believes to have sufficient basis of fact.

The conception of a passive rôle for the capillaries in regard to the flow of blood through them is no longer tenable. Landis⁶ states:

Krogh and Lewis have summarized an impressive mass of evidence showing that the capillary vessels are independently contractile and capable of responding individually in a delicate manner to the circulatory needs of the immediately adjacent tissue.

Apparently Krogh⁵ is of the opinion that independent contractility is of the greatest importance to the regulation of blood flow, admitting that arteriolar in-flow and increase in venous pressure do affect the balance but that contractility is capable of overcoming any possible increase in pressure from these causes.

Duryee and Wright attempted to obtain a definite impression of the flow of blood through these vessels. To do so they employed a "two minute flow test." The capillary is observed under the microscope, and the number of seconds of stoppage and flow are noted. Under average normal conditions the blood will cease to flow after from ten to twenty seconds of the two minute period.

Landis has directly measured capillary pressure⁶ in both the arteriolar and the venous capillary limbs. He has found that the fall

3. Wright, I. S., and Duryee, A. W.: *The Human Capillaries in Health and Disease*, Arch. Int. Med. **52**:545 (Oct.) 1933.

4. Kuntz, Albert: *The Autonomic Nervous System*, Philadelphia, Lea & Febiger, 1934.

5. Krogh, A.: *The Anatomy and Physiology of the Capillaries*, New Haven, Conn., Yale University Press, 1929.

6. Landis, E. M.: *Capillary Pressure and Capillary Permeability*, Physiol. Rev. **14**:3 (July) 1934.

in pressure does not cease at the arteriolar junction but continues through the capillary network and under conditions of arteriolar dilatation may even extend to the venules. From 20 to 30 per cent of the peripheral resistance to blood flow is located in the capillaries. The pressure decreases slightly in the larger arteries; the gradient is steepest in the arterioles but continues through the capillaries. By his method of microcannulation Landis has found the average pressure in the arteriolar capillaries of the nail fold in man to be 43.5 cm. of water with a pressure of 16.5 cm. of water in the venous capillary. This method requires a skill and technic which prohibit its use as a routine measure. The Danzer and Hooker indirect method is considered suitable by Duryee and Wright.²

Capillary pressure is an extremely variable quantity, varying from moment to moment in the same and different vessels. Arteriolar constriction increases peripheral resistance, and capillary pressure falls. It rises during hyperemia caused by heat, and in the presence of histamine and acute inflammation. Under these conditions the observed blood flow becomes more rapid, and pulsations become apparent with an increase in pulse pressure. It is interesting to note that in persons with Raynaud's disease the capillary pressure was found to be below 7 or 8 mm. of mercury during the paroxysm with a very small pulse pressure, but during the phase of relaxation Landis found that it might rise to 40 mm. of mercury with a very high pulse pressure.

According to these observations the relation of blood pressure in the capillaries to the rate of flow is often very close, and the rhythmic increase with cardiac systole may penetrate to the venous capillaries. Cold first diminishes the pressure, which later rises with reactive hyperemia.

Another factor which affects the pressure in the capillaries is the obstruction to outflow offered by an increase in venous pressure. It is higher in dependent portions of the body owing to the hydrostatic pressure of vertically located veins. It is most constant in the hand when it is above the level of the base of the heart and higher when the hand is below that level.

In regard to the interpretation of observations on the moving column of cells in the capillaries with projected light, by means of which the walls of these minute vessels are not visible, Krogh⁵ cautions against the repeated errors made by interpreting gaps in the column of cells and overfilled portions of the vessel as peristaltic waves. He comments on the fact that the "theories in regard to 'peripheral hearts' have been cropping up again and again and are even now seriously discussed and refuted." Wright and Duryee³ are in agreement with Kling-Müller on this point, that the so-called peristaltic waves in the capillaries are no more than gaps in the columns of red cells.

The importance and the present state of the knowledge of the essential function of the capillaries, the exchange of substances between the blood and body tissues, are admirably reviewed by Landis.⁶

THE ARTERIOVENOUS ANASTOMOSES

Arteriovenous communications which are capable of short-circuiting the capillaries were first described anatomically by Sucquet in 1862. Heimberger⁷ was able to observe such connections in the fingers of persons having very delicate skin. These channels are usually closed and open when there is a demand for the rapid movement of blood. Krogh⁸ is of the opinion that the main function of these vessels is to supply enough blood to the projecting parts of warm-blooded animals to supply heat when the animals are exposed to low temperature.

In addition, Wright⁸ has observed small anastomosing vessels which connect different segments of the capillary loop. They may connect the arterial limb with the venous or two portions of the venous loop. The blood may cease to flow through these connections while it still flows through the loop. Wright believes that these are probably residual vessels from the arciform capillaries of early infancy. They are few and are not to be confused with the arteriovenous shunt.

Grant and Bland⁹ emphasize the importance of the arteriovenous anastomoses and the part they play in the vascular reactions of the extremities. The authors are in agreement with Krogh that the chief function of these structures in man and in animals is to maintain the temperature of exposed parts in which they occur.

Anastomoses are present in the fingers and are particularly numerous in the distal portions but do occur in the sole and palm, all locations in which the hyperemic reactions to cold are most marked.

However, from their limited distribution it seems unlikely that they can be more than a minor factor in the regulation of body temperature in man, who has other mechanisms more effective for the purpose.⁹ In the rabbit's ear this function is important. But it is apparent that these anastomoses must be taken into consideration in dealing with the peripheral circulation in whatever areas they do occur because of their numbers as well as their activity.

7. Heimberger, H.: Beiträge zur Physiologie der menschlichen Capillaren, *Ztschr. f. d. ges. exper. Med.* **56**:519, 1925.

8. Wright, I. S.: Intracapillary Anastomoses, *J. Clin. Investigation* **2**:835 (July) 1932.

9. Grant, R. T., and Bland, E. F.: Observations on Arteriovenous Anastomoses in the Human Skin and in Bird's Foot with Special Reference to the Reaction to Cold, *Heart* **15**:385 (July) 1931.

Popoff¹⁰ has made careful anatomic and histologic studies of the arteriovenous anastomoses in man in normal and in pathologic conditions. The anastomoses are found almost exclusively over the ventral surfaces of the hands and feet and are constantly present in the region of the nail bed and in the tips of the fingers, the palmar surfaces of the first, second and third phalanges and the thenar and hypothenar eminences of the hand. Their distribution in the foot corresponds to that in the hand. In the skin they are located a little deeper than the web of subpapillary arteries and veins. They are uniform in appearance, with a narrow and irregular lumen. The layers which overlie the endothelium are indistinct but apparently consist of a muscular coat with inner longitudinal and outer circular layers. Numerous non-medullated nerve fibrils lie in the collagenous outer zone. The collecting veins into which these vessels drain are characterized by a thin wall almost devoid of muscular cells. These veins surround the arteriovenous canals in the form of plexuses. The primary collecting veins open into the subpapillary veins.

The terminology employed by Popoff is distinct. The entire anastomotic unit is called the glomus. It consists of the afferent artery, the arteriovenous anastomosis (called the Sucquet-Hoyer canal), the neuroreticular and vascular structures around the canal, the outer collagenous tissue and the primary collecting veins. Capillaries are richly supplied to the collagenous area surrounding the canals. These apparently arise from preglomic arterioles given off from the afferent artery and finally enter into the limbs of the small plexus of veins surrounding the anastomosis, the primary collecting veins. Beyond the glomus the artery divides in the subpapillary layer into the arterioles and capillaries of the stratum capillare.

The beginning of the Sucquet-Hoyer canal is marked by the presence in the afferent artery of cushion-like endothelial muscular elevations, the function of which is to direct the blood flow into the Sucquet-Hoyer canals and preglomic arterioles.

The theory of function of the glomus, according to Popoff, is the regulation of heat locally as well as the regulation of body temperature as a whole. With exposure of the hand to cold the blood is diverted from the capillaries through the anastomoses into the collecting veins with a highly developed surface area, thus maintaining a constant local temperature. When the glomic system is fully opened as a result of the general reaction for the dispersion of heat, an enormous flow of blood may take place through the digits, allowing for the rapid loss of heat, which is limited by the very slow flow through the capillaries. The

10. Popoff, N. W.: The Digital Vascular System, with Reference to the State of the Glomus in Inflammation, Arteriosclerotic Gangrene, Diabetic Gangrene, Thrombo-Angiitis Obliterans and Supernumerary Digits in Man, *Arch. Path.* 18:295 (Sept.) 1934.

glomus can also relieve the peripheral arterial system if the pressure within becomes very high, by shunting the blood across to the deep veins. In a like manner capillary stasis can be relieved. In man these anastomoses are under the control of vasomotor nerves.

The digital glomus is formed only after birth and in the aged undergoes atrophy. As the result of pathologic destruction a new canal can develop from one of the preglomic arterioles.

In cases of arteriosclerotic gangrene and diabetic gangrene two different processes present themselves. In the first there is hyaline degeneration of the afferent artery, while in cases of diabetic gangrene the Sucquet-Hoyer canal and the preglomic arterioles are involved primarily.

In cases of thrombo-angiitis obliterans there are no primary thrombotic or inflammatory reactions. A new idea as to the pathogenesis of the disease is presented in the discovery of many newly developed anastomoses between arteries and veins and between veins themselves. These anastomoses are pathologic and differ entirely from those of the normal glomus. They are purposeless and detrimental to the circulation.

THE NERVE SUPPLY OF THE BLOOD VESSELS

The essential nerve supply ¹¹ to the blood vessels of the extremities is derived from that part of the autonomic nervous system which from its location in the long chain of ganglionated nerve cords extending vertically through the abdomen, thorax and neck is called the thoracolumbar or sympathetic portion. Preganglionic fibers arise from nuclei in the gray matter of the spinal cord, travel through the ventral roots and by way of the white rami enter the sympathetic system, where they turn either upward or downward and run for varying distances before terminating in synaptic relationship with the nerve cells of the sympathetic ganglions. From this point the postganglionic fiber begins, and it emerges from the sympathetic ganglion through the gray rami communicantes to the spinal nerves through which the postganglionic fibers then travel to supply the blood vessels, the secretory activity of the sweat glands and the pilomotor function of the hair follicles.

The cervical sympathetic trunk is composed almost exclusively of preganglionic efferent fibers derived through the white rami from the upper thoracic nerves and ascends to terminate in the cervical sympathetic ganglions. The lumbar and sacral portions of the trunk are composed in the major part of descending fibers from the white rami of the lower thoracic and upper lumbar spinal nerves.

It is important to note that the nerve supply to the arteries of the extremities is carried by the somatic nerves and segmentally distributed

11. Ranson, S. W.: *The Anatomy of the Autonomic Nervous System with Special Reference to the Innervation of the Skeletal Muscles and Blood Vessels*, Ann. Int. Med. 6:1013 (Feb.) 1933.

to the blood vessels. The work of Ranson¹¹ and Kuntz⁴ as well as the observations of many others is conclusive on this point. Ranson states that branches from the celiac ganglion and the plexuses which follow the aorta continue to the iliac vessels, where small plexuses are formed. Branches from these extend down the femoral arteries for a relatively short distance to terminate. They are relatively few in number and can be followed no farther. This is apparently the only exception. Beyond this point the vascular nerves are carried by the somatic nerves and are thereafter supplied to all the vessels, including the capillaries, in such a manner that the vascular distribution of nerve supply corresponds closely to the sensory distribution of nerves in the skin of both the upper and the lower extremities so that interruption of the sympathetic system by anesthetization of, for example, the median nerve produces peripheral loss of vascular tone in an area of the skin corresponding to the sensory distribution of that nerve in the hand.

That the sympathetic nerves to the blood vessels are vasoconstrictor has long been known, but to what extent the peripheral blood vessels are supplied by vasodilator nerves is uncertain.⁴

Lewis and Pickering¹² report experimental data which they believe indicate the existence of vasodilator as well as vasoconstrictor fibers in the sympathetic nerves to the extremities. They found that in normal persons vasodilatation could be observed in the hands when they were exposed to a room temperature of from 14 to 16 C. if the body was enclosed in a warm chamber. There would be a marked rise in the temperature of the fingers and hands when the body was warmed. In a patient with Raynaud's disease ulnar interruption of the sympathetic nerves by the injection of a local anesthetic failed to bring about vasodilatation in the area supplied at the environmental temperature of from 14 to 16 C. If, however, the same patient's body was placed in the warm chamber with the hands exposed to the same environmental temperature, complete vasodilatation took place in the hand except in the finger the nerve supply of which was blocked. Thus Lewis and Pickering concluded that simply inhibition of vasoconstriction cannot account for these variations and that the presence of vasodilator fibers in the sympathetic nerves of man must be admitted.

McDowell¹³ states that the nerve supply to the capillaries has been repeatedly demonstrated, but that the full physiologic significance of this fact has taken many years to be appreciated. The vasoconstrictor

12. Lewis, T., and Pickering, G. W.: Vasodilatation in the Limbs in Response to the Warming of the Body with Evidence for Sympathetic Vasodilator Nerves in Man, *Heart* **16**:33, 1931.

13. McDowell, R. J. S.: Nervous Control of the Blood Vessels, *Physiol. Rev.* **15**:98 (Jan.) 1935.

nerves affect both the arterioles and the capillaries as well as the larger vessels. It is also certain that veins are capable of constriction, although the mechanism by which this occurs is not discussed. It seems that the veins must have a connection with the nervous system.

The more than occasional failure to obtain permanent complete peripheral vasodilatation in man following sympathetic ganglionectomy and ramisectomy, particularly in the upper extremities, is usually explained by failure to interrupt all the sympathetic constrictor fibers because of anatomic difficulties and variations in the location and form of the ganglions.¹⁴ In the lower extremities results seem to be more permanent in the majority of instances.

That the peripheral vessels are capable of maintaining a degree of tone after a certain interval independent of their nerve supply in animals has long been known. Whether or not this applies to man has been questioned.⁴

In a carefully studied case¹⁵ in which there was complete peripheral vasodilatation with all the concomitant signs of removal of the superior cervical and second thoracic sympathetic ganglions, the tone of the peripheral vessels returned to the normal preoperative level within twenty-one days. A digital plethysmograph was employed as a direct measure of the circulation. The temperature of the skin remained elevated, the function of the sweat glands remained inhibited, and Horner's syndrome persisted. It was possible to induce vasodilatation in the digits by immersion of the hand in hot water to the same degree as that of the normal side. Following the induction of artificial fever there was the usual vasodilatation in the normal digits; on the side on which sympathectomy has been performed there was no vasodilator response. This would also indicate that the denervation was complete, since no peripheral response to the release of central tone was possible, as it occurred in the normal side. This result is in keeping with the results of experiments on animals in which preoperative tone is reestablished in from ten to fourteen days after sympathectomy, and it is not logical to assume that the control of vascular tone is much different in man from that in animals. Also, the increased temperature of the skin, usually considered to be an index of increased flow of blood to the part, following sympathetic ganglionectomy may be largely due to a loss of part of the heat-regulating mechanism.

14. Adson, A. W.: The Results of Sympathectomy in the Treatment of Peripheral Vascular Diseases, Hirschsprung's Disease and Cord Bladder, *Ann. Int. Med.* **6**:1044 (Feb.) 1933.

15. Johnson, C. A.; Scupham, G. W., and Gilbert, N. C.: Studies in Peripheral Vascular Phenomena: II. Observations on Peripheral Circulatory Changes Following Unilateral Cervical Ganglionectomy and Ramisectomy, *Surg., Gynec. & Obst.* **55**:737 (Dec.) 1932.

Coller and Maddock¹⁶ comment on the fact that interruption of the sympathetic pathway results in the exclusion of the extremity in which interruption was effected from participation in the regulation of the heat of the body by interruption of the vasoconstrictor effect by which the dispersion of heat is prevented. It is the loss of this function which they believe results in an increased flow of blood to the extremity.

In contrast to this, Adson¹⁴ cites the observations of Waggoner on the vessels of the fundus after cervicothoracoganglionectomy and resection of the trunk in Raynaud's disease. Both the arteries and the veins dilate from one and one-third to one and one-half times their preoperative diameter, and the dilatation is permanent. He states that the increased flow of blood as indicated by the increased elimination of heat continues and does not recede to the preoperative level. The capillaries are seen to be smaller in diameter than those noted in the cyanotic phase of Raynaud's disease, but the stream of corpuscles is seen to flow much faster.

McDowell,¹⁵ in an excellent review of the subject, states that even after all the nerves to a part are cut the peripheral vessels in animals in time recover their normal caliber. In regard to the vessels responsible for the recovery, he cites the work of Herrick, Essex and Baldes to show that the large vessels are not concerned with the recovery of tone. Their observations thirty-four months after sympathectomy revealed an increased flow of blood in the femoral artery of the side on which the operation was performed. McDowell believes that the capillaries themselves seem to be the most likely location for the opposing effect, which he thinks is probably the result of the action of chemical agents normally present in the circulating blood. This is a direct effect on vascular tone, and the vessels are more sensitive to chemical influences soon after denervation. When the nerves fully degenerate the reaction disappears.

McDowell also states that it is difficult to imagine that there is a fundamental difference between man and animals in regard to sympathetic denervation, although clinical evidence in many instances seems to point in this direction.

In regard to the chemical and hormonal effects on the blood vessels after sympathectomy in man, Freeman, Smithwick and White¹⁷ found

16. Coller, F. A., and Maddock, W. G.: The Function of Peripheral Vasoconstriction, *Ann. Surg.* **100**:983 (Nov.) 1934.

17. Freeman, N. E.; Smithwick, R. H., and White, J. C.: Reactions of the Blood Vessels of the Human Extremity Sensitized by Sympathectomy to Adrenalin and to Adrenal Secretion Resulting from Insulin Hypoglycemia, *Am. J. Physiol.* **107**:529 (March) 1934. Smithwick, R. H.; Freeman, N. E., and White, J. C.: The Effect of Epinephrine on the Sympathectomized Human Extremity: An Additional Cause for Failure of Operations for Raynaud's Disease, *Arch. Surg.* **29**:759 (Nov.) 1934.

that the blood vessels of the extremities become more sensitive to epinephrine after sympathectomy. The increased sensitivity develops from six to eight days after paralysis and does not occur in acutely denervated areas following immediately after nerve block by a local anesthetic.

The intravenous infusion of a 1:250,000 solution of epinephrine, which causes little change in the normal side, is sufficient to cause a lowering of surface temperature as much as 15 F. on the denervated side. The same thing happens when the adrenal glands are stimulated by hypoglycemia caused by insulin. Identical vasospastic phenomena which occur in sympathectomized cats and in rabbits with hypoglycemia caused by insulin can be abolished by adrenal denervation.

THE FUNCTIONS OF VASOCONSTRICTION AND VASODILATATION

It is by constriction that the normal tone of the peripheral vessels is maintained. The degree is constantly fluctuating in response to environmental changes in temperature, internal production of heat and emotional reactions. Perhaps the most constant effect is that of response to the requirements of the body for the maintenance or dispersal of heat. Lewis and Pickering¹² have shown that when a person lightly clad is exposed to an environmental temperature of from 16 to 18 C. constriction of the vessels of the skin of the hands and feet is in high degree. An increase in the environmental temperature to a higher level results in release with an increased surface temperature. The vasodilatation which occurs is accomplished in part by a direct effect on the vessels of the skin and by the effect of the warmed blood on the central temperature-regulating mechanism which results in vasodilatation by action through the central nervous system.

The authors found that if the body was warmed while the hands were exposed to a temperature of from 14 to 16 C. vasodilatation took place in the hands. The finger-tips warmed first, then the base and finally the hand. Cooling occurred in the same order. The response of dilatation occurs earlier in the fingers than in the toes. Exceptionally vasodilatation may fail to occur in the toes. This delayed response is interpreted not as a difference in vascular tone but as a difference in the intensity of the vasomotor relaxation in the upper and lower extremities. With warming of the body to a higher degree or increase in the environmental temperature relaxation could occur.

Normal vascular reaction to cold has been studied by Sir Thomas Lewis.¹⁸ This reaction is expressed locally by vasodilatation preceded by constriction when one finger is immersed in cold water for a period of from five to ten minutes. The vasodilatation continues during

18. Lewis, T.: Observations upon the Reaction of the Vessels of the Human Skin to Cold, *Heart* 15:177, 1931.

immersion, often giving rise to a phasic rise and fall of temperature. After the finger is removed the temperature rises well above that of the uncooled digits. The temperature rises gradually and then falls slowly. The lower the temperature the more marked is the reaction. This reaction can be elicited from the fingers, toes, ears and parts of the face. It is considered that this reaction is the result of an axon reflex of a sensory nerve which is activated by the release of the so-called H substance of the skin. The function of this mechanism is the protection of exposed parts from injury by exposure to cold.

The same type of reaction occurs as the result of exposure outdoors provided the body is kept warm and only the hands are exposed. At first the temperature of the finger falls to near that of the environmental temperature; this is followed by a rise after an interval of about one hour to a level of from 4 to 13 C. above the minimum. The more quickly the fall occurs, the more rapid is the reactive vasodilatation. The fingers are painful while the temperature is low and rapidly become comfortable as soon as the reaction sets in.

This reaction fails to occur if the body is not kept warm. If larger surfaces of the body are cooled, then general vasomotor tone is increased and local reactive hyperemia cannot occur. If the finger is immersed in ice-water while the opposite arm is likewise immersed in water at a temperature of from 15 to 25 C. at a room temperature of from 19 to 21 C., the reaction seldom occurs. If the temperature of the bath of the opposite arm is increased to 30 C., the reactive hyperemia is invariable.

When the entire body or larger portions of it are exposed to cold or protection is inadequate, the blood vessels of the skin become constricted. The cooling of one hand when the other is immersed in ice water has long been known but has been usually considered to be a vascular reflex from the skin by the stimulus of cold. Pickering¹⁹ states that the whole surface of the skin reacts in the same way. He says: "Vasoconstriction arising reflexly from a cold stimulus applied to the skin seems to be securely established by the work of Franck," but he advances experimental proof that this is not the sole mechanism, although his observations do confirm those of Franck. The mechanism is of a dual nature. In addition to the direct stimulation which gives rise reflexly to cutaneous vasoconstriction, which he has found to be of short duration and which is an immediate response, the essential mechanism is the result of the effect of the cooled blood, flowing from the cold part, on the central temperature-regulating mechanism, through which general vasoconstriction occurs.

19. Pickering, G. W.: Vasomotor Regulation of Heat Loss from the Human Skin in Relation to External Temperature, *Heart* 16:115, 1932.

Pickering has further shown that the effect of the application of heat brings about essentially the same type of response. General vasodilatation follows an increase in the environmental temperature, and likewise the exposure of one member to increased temperature by immersion in warm water results in general vasodilatation, but the mechanism by which this occurs is single. There has been no proof advanced, according to Pickering,¹⁹ that a central nervous reflex plays any part in the general vasodilatation which follows, but all the experimental evidence which he has accumulated indicates that the phenomenon is a direct effect on the temperature-regulating mechanism (not the temperature center) by the effect of the warmed blood flowing from the warmed part, which results in a general vasomotor release of tone with general vasodilatation in the attempt to increase the elimination of heat from the surface of the body.

The local effect of heat on the blood vessels is in part a direct action on the walls of the vessels, which respond by dilatation, and in part the result of the increased amount of warmed blood from the heated extremity on the central temperature-regulating mechanism. It seems probable that the local effect is the direct release of vasoconstrictor tone which exceeds the normal constrictor tone exerted by the vasomotor system. In addition to the effect on the larger vessels, those of the skin are effected directly by the release of the familiar H substance, especially following the injury which is produced by immersion in water at higher temperatures.

After permanent interruption of the sympathetic pathway by ganglionectomy it has been possible to demonstrate dilatation of the digital arteries after immersion of the hand in hot water by observation of the increase in pulsations of these vessels, which could then be abolished by cold.²⁰ The same reactions have been observed by means of plethysmographic measurements of circulation following cervico-dorsal sympathetic ganglionectomy and ramisectomy. Essentially the same degree of vasodilatation could be induced in the denervated hand as in the normal hand by direct immersion in hot water. Induction of fever by the injection of typhoid vaccine intravenously resulted in no change in the vessels of the denervated finger, while in the normal finger, the usual vasodilatation took place.¹⁵

Maddock and Coller,²¹ in a more recent publication, call attention to the important part played by the extremities in the control of body temperature. The surface of the skin dissipates 76 per cent of the total

20. Lewis, T., and Landis, E. M.: Some Physiological Effects on Sympathetic Ganglionectomy in the Human Being and Its Effect in Raynaud's Malady, *Heart* **15**:151, 1930.

21. Maddock, W. G., and Coller, F. A.: The Rôle of Extremities in the Dissipation of Heat, *Am. J. Physiol.* **106**:589 (Dec.) 1933.

heat produced by conduction, convection and radiation. Twenty-four per cent is eliminated by the vaporization of water from the surface and by the lungs. This is at comfortable environmental temperatures. With an increase in the environmental temperature or with hard labor, sufficient heat cannot be eliminated in this way, and vaporization increases so that it may account for almost all the heat lost.

Maddock and Collier consider that the temperature of the skin at any one point is a resultant of the heat brought to it largely by its blood supply and the heat lost from its surface. There is a gradient from the deep tissues of the extremity to its surface. When the skin is cool there is a depth of from 3 to 5 cm. where the temperature is less than that of the blood. The gradient is diminished by exposure to heat and increased by cold.

With these considerations in mind, under carefully controlled conditions Maddock and Collier were able to show a marked increase in the surface temperature of the extremities above that of the rest of the body, demonstrating a much greater degree of peripheral vasodilatation here than on the head or trunk. The same result was apparent with changes in the internal production of heat when the temperature and humidity were kept constant. Under these conditions the temperature of the toe showed a straight line relationship to the basal production of heat per unit of surface area.

The extremities show great variations in vasoconstrictor tone because they are normally called on to take a major part in the conservation or elimination of heat, a part they are particularly adapted for as they contain no vital organ. They supply 65 per cent of the total body surface and are thrust out into their environment in such a manner as to make the dissipation of heat effective.

An interesting comment is made in regard to the normal tone of the vessels of the extremities resulting from the heat-conservation mechanism being confused with angiospasm.

DIAGNOSTIC METHODS

In many cases a diagnosis of peripheral vascular disease can be made without the use of special equipment. In some cases all the information obtainable fails to allow a conclusive decision. This is particularly true in the differentiation of various types of circulatory impairment. Reid²² comments on the importance of early diagnosis of vascular disease in the extremities, because by relatively simple therapeutic measures applied at an early stage many persons may be spared the consequences of gangrene. The means for estimating the circu-

22. Reid, M. R.: *Diagnosis and Treatment of Peripheral Vascular Diseases*, Am. J. Surg. 24:11 (April) 1934.

latory efficiency are as accurate as those for the heart and kidneys and should be included in all routine and general physical examinations.²²

Most of the methods of examination by inspection and palpation have been described in detail in earlier publications by Buerger,²³ Silbert,²⁴ Brown²⁵ and many others. Particularly those subject to errors of interpretation and the more recent methods are considered here.

The importance of careful general examination has been emphasized many times.²⁶ This is particularly true in regard to consideration of the cardiovascular system. Impairment of cardiac function, particularly with disorders of mechanism, may be responsible for the rapid exaggeration of symptoms referable to structural arterial diseases in the extremities. Metabolic and infectious diseases are frequently the cause of circulatory impairment or may simulate impairment when circulation is adequate.

Disease of the central or peripheral nervous system is capable of simulating vascular disease and is often a common cause of peripheral vasospastic phenomena. The Raynaud syndrome is not uncommon as a manifestation of other diseases, including scleroderma and rheumatoid arthritis, while acrocyanosis is nearly always secondary. While vascular disorders have frequently been mistaken for static orthopedic diseases, the converse is also true.

Obliterating arteriosclerotic disease is frequently part of general arteriosclerosis, and cerebral, cardiac and other manifestations may be simultaneous. While the phenomena of hypertension are usually visceral, there are occasionally peripheral accidents. Thrombo-angiitis obliterans is essentially a peripheral vascular disease, but visceral vascular disease has been reported with increasing frequency, while the opposite is true of periarteritis nodosa. Severe anemia, by pallor and even by intermittent claudication,²⁷ may simulate obstructive disease, while in polycythemia both thrombosis and vasodilator phenomena are common.

23. Buerger, Leo: *The Circulatory Disturbances of the Extremities Including Gangrene: Vasomotor and Trophic Disorders*, Philadelphia, W. B. Saunders Company, 1924.

24. Silbert, Samuel: *Studies in Thrombo-Angiitis Obliterans (Buerger): II. The Effectiveness of Therapeutic Procedures*, J. A. M. A. **89**:964 (Sept. 17) 1927.

25. Brown, G. E.; Allen, E. V., and Mahorner, H. R.: *Thrombo-Angiitis Obliterans*, Philadelphia, W. B. Saunders Company, 1928.

26. (a) de Takáts, Géza, and Mackenzie, W. D.: *Diagnosis and Treatment of the Circulatory Disturbances of the Extremities*, Surg., Gynec. & Obst. **58**:655 (March) 1934. (b) Weiss, Soma: *Circulatory Disturbances of the Extremities: Medical Aspects*, New England J. Med. **209**:267 (Aug. 10) 1933.

27. (a) Pickering, G. W.: *On the Clinical Recognition of Structural Disease of the Peripheral Blood Vessels*, Brit. M. J. **2**:1106 (Dec. 16) 1933. (b) Lewis, T.; Pickering, G. W., and Rothschild, Paul: *Observations upon Muscular Pain in Intermittent Claudication*, Heart **15**:359, 1931.

Thus it becomes increasingly evident that while essential progress has been made in the study of peripheral vascular disease, its consideration in relation to visceral disease should be appreciated. The difference in environmental relationship between the blood vessels of the extremities and those of the viscera as well as a difference in their functions renders them more susceptible to the development of both functional and organic disease.

Abnormalities of Appearance.—In a discussion of the clinical recognition of structural diseases of the blood vessels of the extremities, Pickering ^{27a} summarizes the abnormalities of appearance. These are, essentially, gangrene, which is the result of prolonged interruption of blood flow, and indolent ulceration, which follows impairment of the blood supply, spasmodic or organic, often associated with chronic infection. The abnormalities of color may be either change in normal depth or change in tint. They are varied, subject to errors of interpretation and yet important.

In the absence of severe anemia, local pallor indicates that the superficial vessels are empty. It usually occurs when blood is massaged out of a part and inflow is impaired by organic or spasmodic constriction of the vessels. Conspicuous pallor when a limb is maintained above the level of the heart strongly suggests structural impairment, because blood fails to enter it from the arterial side while it drains out into the venous circulation. If rapid cyanosis occurs when the limb is suddenly changed to a dependent position, the significance is increased. Persistent pallor may occur when the inflow of blood is limited to an extreme degree or the superficial vessels are constricted, as in Raynaud's disease during the pallid stage of the paroxysm. When the superficial vessels are not constricted, the color is dependent on backflow into the capillaries of the veins. Pallid skin is always cold if the color is dependent on impaired arterial inflow.

Increased depth of color, rubor, is due to dilatation of the capillaries and small vessels of the skin as the result of local injury by impaired blood supply, continued cold, low grade or chronic inflammation, ultra-violet irradiation or mechanical injury. Lewis ²⁸ points out that redness of the skin does not indicate of itself an increased blood supply, because mere dilatation of the capillaries at the surface, even with considerable impairment of inflow, may result in redness. In this case it is associated with decreased skin temperature. Redness with normal or increased surface temperature is compatible with normal or increased circulation.

Local cyanosis is due to local slowing of the blood stream relative to the oxygen requirements of the skin. In a cold skin cyanosis may

28. Lewis, T.: Clinical Observation and Experiments Relating to Burning Pain in the Extremities and So-Called Erythromelalgia in Particular, Clin. Sc. 1:175 (Dec.) 1933.

occur as a result of spasmodic constriction of arterioles yet capable of dilating. If the limb is warmed the vessels may be assumed to be dilated, and cyanosis here is strong presumptive evidence of structural disease above.

Postural changes in color are common in persons with organic disease of the arteries. Deepening of cyanosis of the skin when a limb is dependent is commonly due to stasis in the toneless superficial vessels with filling consequent on the static increase in venous pressure. In the event of rubor with dependence the change may be merely due to dilatation of the vessels of the skin consequent on local injury, but with cyanosis it is usually due to some impairment of circulation in addition. Marked variations in tint may be present between marked rubor and extreme cyanosis.

In appreciation of the value of observation of color and to establish an objective means of recording such variations, the color chart of Lewis²⁸ is applicable. However, extreme care must be exercised in the interpretation applied to variations in color. Local cutaneous injury or inflammation, impaired arterial inflow and obstructed venous outflow must all be considered. The rate of return of color produced by blanching of the skin by pressure of the finger is not reliable as a test of efficiency of the circulation.

Palpation of the Vessels.—The local condition of blood vessels as determined by inspection and palpation is an important and widely used criterion of the condition of the circulation. Arterial pulsations determined by palpation with the finger are open to certain errors of interpretation. It is generally assumed that when pulsation is present in the dorsalis pedis and posterior tibial arteries the arterial circulation is intact. Pickering^{27a} points out that pulsation may be retained in the larger vessels when smaller distal vessels are occluded. Also, circulation may be nearly normal with the absence of pulsation as in coarctation of the aorta or impaired cardiac function. In extreme senile arteriosclerosis pulsations may be extremely weak or absent owing to sclerosis of the wall of the vessel, yet with entirely adequate circulation. Pickering^{27a} also emphasizes the importance of temperature. In a very cold extremity pulsations may be very feeble. He states: "The failure of pulsation in an artery of a limb when body and limb are warm is the most certain sign we possess of structural disease of that vessel."

The frequency of anatomic variations from the normal has been discussed by Reich,²⁹ who states that all writers have referred to the pulses of the foot as a cardinal criterion of peripheral circulatory efficiency. Buerger thought that absence of the pulse occurs in only

29. Reich, R. S.: The Pulses of the Foot, *Ann. Surg.* **99**:613 (April) 1934.

0.5 per cent of normal persons and therefore is a finding of paramount importance in persons with peripheral vascular disease.

In observations on 500 normal healthy persons the dorsalis pedis artery was absent in 4 per cent and the posterior tibial artery in 5 per cent, while in another 8 per cent the dorsalis pedis artery was found in other than its usual position. It is evident, then, that the absence of these pulses cannot be interpreted as being due to disease without other confirmatory evidence.

In addition, extravascular factors diminish the ease with which these pulses can be felt. Edema, adiposity, tendons and ligaments interfere.

Reich says that variations are common because these vessels are of relatively recent phylogenetic origin. In primates other than man the popliteal artery ends in vessels in the muscle while the foot is supplied by a direct continuation of the femoral artery, the saphenous artery, which is absent in man. In man alone of all the primates is found the complete pattern of the new connections between the popliteal artery and its distribution on the dorsum and sole of the foot.

Visible capillary pulsations after warming an extremity by immersion in hot water are good evidence that circulation to the exposed part is intact.²⁷ Absence does not invariably indicate occlusion. Veins likewise share in the vascular relaxation caused by local heat, and superficial venous plexuses can be demonstrated by immersion in water at from 35 to 40 C., especially with the part dependent, or by obstruction of the veins by a pressure of from 60 to 70 mm. of mercury.

In the upper extremity the vessels show less variation, although the ulnar artery is less readily palpable. The presence of pulsation in these vessels likewise does not exclude organic disease because of the extensive blood supply to the hand and fingers. Pulsation of the digital arteries can usually be felt in normal persons after the immersion of the hand in hot water (40 C.), but again, the absence of pulsation without other corroborative evidence does not always indicate occlusion.²⁷ Allen's test is reliable, particularly when there is a striking difference in the reactions in the two hands. It is a test for the patency of the circulation of the radial and ulnar arteries beyond the wrist.

Ischemia.—The appearance of intermittent claudication in the absence of severe anemia may be taken as an indication that structural disease of the vessels is present.²⁷ In order to avoid possible errors in interpretation, Lewis, Pickering and Rothschild ^{27b} used an exercise test based on the following observation: The circulation of the leg of a healthy person is interrupted, and the ankle joint is repeatedly and fully extended against resistance at the rate of one complete movement a second. Pain appears in the muscles of the calf if the ankle is flexed; against extension pain appears in the anterior tibial muscles. The pain

appears in from twenty to thirty seconds and disappears in five seconds or less after circulation is released. If a patient with diseased vessels works his leg in the same way without circulatory arrest, then the time taken for the pain to appear, become unbearable and disappear after exercise provides a guide for the adequacy of muscular blood supply. As a basis for comparison, the time taken for the occurrence of these phenomena when the circulation is arrested can be estimated if a period of more than fifteen minutes is allowed to elapse between tests.

Samuels ³⁰ has described a test for plantar ischemia which is of considerable value in determining inadequacy of arterial inflow to the foot. With the patient recumbent and the legs in the vertical position the feet are flexed and extended at the ankle. In addition to pain or fatigue, conspicuous pallor of the plantar surfaces occurs if the arterial circulation is inadequate. These findings are particularly important if they occur unilaterally.

Reactive Hyperemia.—The test for reactive hyperemia, if properly performed, is considered by Pickering ^{27a} to be as delicate as any single test yet devised and requires no apparatus but a sphygmomanometer. Two precautions are necessary. The vessels must be dilated to the maximum, which can be assured by having the body quite warm and the limbs to be tested warm enough to maintain maximum dilatation of the cutaneous vessels. The vessels of the skin must be emptied of blood before the circulation is arrested. In performing the test the limbs can be warmed by the application of external heat or immersion in water at from 35 to 40 C. They are lifted out of the water and elevated with the patient recumbent to empty the vessels. Circulation is then arrested by the application of a sphygmomanometer cuff above the level of systolic blood pressure for the limb. The limb is then lowered and kept warm. After four and one-half minutes it is laid horizontal in good light. One-half minute later the circulation is released. A flush appears in the extremity and its course is observed. When the vessels are patent, as in normal persons or in persons with uncomplicated Raynaud's disease or acrocyanosis, the flush reaches the digits in less than five seconds. It is bright and reaches maximum intensity in less than fifteen seconds and fades quickly. In structural disease the flush spreads slowly, is patchy or mottled and is considerably delayed to the tips of the digits, even to a minute or more. The flush is somewhat cyanotic in tint and lasts longer. All patients known to have structural disease have, in the experience of Pickering, shown an abnormal reaction indicating obstruction to the inflow of arterial blood to the vessels of the skin.

30. Samuels, S. S.: The Early Diagnosis of Thrombo-Angiitis Obliterans: A New Diagnostic Sign, J. A. M. A. 92:1571 (May 11) 1929.

Surface Temperature.—It has been said that this is perhaps the most important indication for the determination of the adequacy of blood flow through a limb.^{27a} Certainly it is the most widely used and relied on of the objective means of measurement. The temperature of the skin at any one point is the resultant of the heat brought to it, largely by its blood supply, and the heat lost from its surface.²¹ It is evident that there are wide fluctuations in health, and because of this as well as because of the effect of environmental conditions, observations must be carefully controlled. The blood flow to the skin is of great importance in the maintenance of body temperature. The effect of exposure to cold is, first, a direct action on the superficial arterioles resulting in their constriction and, second, generalized vasoconstriction of the vessels of the skin evoked in part reflexly by stimulation of the skin by cold and in part by action of the cooled blood on the central temperature center. When prolonged or extremely cold short exposures occur, reactive vasodilatation follows. It is assumed that under these conditions the arteriovenous anastomoses also open.⁵ When the air is cool and the entire body is cooled the peripheral vessels are constricted and the skin temperature is low. When this mechanism is no longer adequate to control the temperature of the body with the patient at rest or with minimal internal production of heat, shivering occurs.²¹ The skin is further cooled by evaporation, which is dependent on the amount of moisture on the surface and its rate of evaporation, which in turn is dependent on environmental temperature, relative humidity and air currents.

Increased environmental temperature results in vasodilatation and increased surface temperature. In addition to these environmental factors, there are those dependent on the individual patient, his body temperature, rate of metabolism and emotional reaction, which result in constantly varying vasomotor changes. Yet when these factors are controlled with reasonable care, the skin temperature is a sufficiently reliable guide as to the efficiency of the circulation for practical clinical objective use. It has been shown, however, that observations on skin temperature after sympathectomy are no longer a reliable measure of the circulation because, in part at least, of the abolition of the function of the sweat glands and failure of loss of heat by evaporation.¹⁵

It is apparent, then, that coldness of the extremities alone does not suffice for the diagnosis of arterial disease or spasm. Inequality of temperature between two symmetrical extremities is of the utmost importance if they are similarly treated and exposed for the same length of time to the environment. Unilateral coldness almost always indicates structural disease of the vessels. Rarely, the reverse is true because of the opening of collaterals of the skin and subcutaneous tissues.¹⁹

The temperature gradient is also important. A sudden decrease in temperature from the proximal to the distal portion of an extremity is evidence of impairment of circulation.³¹

Readings of surface temperature are particularly important in observations after the removal of vasoconstrictor tone, which will be considered later.

A rough idea of differences in the surface temperature can be obtained by simple palpation in properly controlled surroundings. Differences of 1 C. can be appreciated, and when it is considered that in cases of obstructive disease there may be variations of 3 degrees or more, such a measure may be of considerable diagnostic value in conjunction with other simple tests. A mercury thermometer of special type has been used by some observers,^{26a} but others consider it unreliable. The most widely used method is that of some form of thermoelectric couple by which accurate readings are quickly obtained.

Calorimetric determinations have been largely supplanted by measurement of skin temperature under controlled conditions.

Oscillometry.—By means of the Pachon oscillometer or instruments of similar type information as to the state of the larger and deeper arteries of the extremities may be obtained.³² Friedlander³³ has noted that the maximum oscillometric phase is variable in many conditions and even in the same person. The form of the oscillogram is important, and Friedlander has noted four distinct types, the normal type and those of arteriosclerosis, hypertension and medial sclerosis. Mixed forms appear in some persons. Oscillograms must be interpreted on the basis of the factors which maintain blood pressure, the force of the cardiac contraction transmitted to the point of observation, the condition of the walls of the blood vessels and the degree of peripheral resistance as well as other uncertain factors, possibly the volume and viscosity of the blood.

Simpson³⁴ has shown the importance of the use of a standard technic. Variations in the application of the cuff often lead to error.³¹ The shape and height of the oscillogram determined at different levels of the same extremity and compared with readings at symmetrical levels

31. (a) Brown, G. E.: *Thrombo-Angiitis Obliterans*, Surg., Gynec. & Obst. **58**:297 (Feb. 15) 1934. (b) de Takáts and Mackenzie.^{26a}

32 Samuels, S. S.: *The Value of Oscillometry in the Study of Circulatory Disturbances of the Extremities*, J. A. M. A. **88**:1780 (June 4) 1927. de Takáts and Mackenzie.^{26a}

33. Friedlander, A. I.: *Studies in Oscillometry*, Am. Heart J. **9**:212 (Dec.) 1933; *Recognition of Types of Arteriosclerosis by Oscillometry*, J. A. M. A. **104**:297 (Jan. 26) 1935.

34. Simpson, S. L.: *Instrumental Methods in the Study of Peripheral Vascular Diseases*, Am. Heart J. **6**:309, 1931.

of the other extremity give a fairly accurate idea of the arterial inflow through the larger arteries. Readings taken above and below arterial occlusions demonstrate the site of the lesion.^{26a} The test does not, however, determine the extent of the collateral circulation. Used in conjunction with other tests, it is of particular value in organic arterial disease.

Comparison with the reaction to histamine made by Kramer³⁵ led him to believe that these tests are nearly parallel in efficiency. It may indicate an efficient circulation in a limb with definitely diseased arteries if the collateral circulation is effective. De Takáts says that the histamine test is capable of determining the extent of collateral circulation, which he thinks is not possible with the oscillometer.

Samuels³² comments on the fact that in some cases of thromboangiitis obliterans in which the readings are zero over a considerable extent of the leg, there is no evidence of impairment of integrity of the tissues. He assumes that in such cases the arterial flow consists of seepage or ooze through canalized vessels or collateral circulation rather than a pulsatile current.

In spite of these and other shortcomings, the oscillometer is capable of giving information concerning the vessels of an extremity as a group which is not obtainable in any other way except perhaps by arteriography.

Plethysmographs.—Johnson³⁶ has introduced a recording plethysmograph of an exceedingly sensitive type which is easily used, compact and simple to operate. It is capable of measuring and supplying a permanent record of the changes of volume in a digit which result from each ventricular contraction with accuracy to 0.002 cc. The instrument consists of a glass cup, which is applied to any digit, with an air conduction system which actuates a bubble of alcohol in a graduated 1 cc. pipet. The movements of the bubble are recorded on a moving strip of electrocardiograph paper together with the volumetric markings on the pipet, which furnish the means of measuring the changes of volume in the digit against the oscillations of the bubble of alcohol. By this method inertia and friction have been reduced to a minimum.

The observations can be employed in the same ways that observations on skin temperature are used both for the determination of the existence of structural disease and angiospastic conditions and for their differentiation with the release of vasoconstrictor tone.¹⁵ The sensitivity of the device is demonstrated by the fact that disturbances in cardiac

35. Kramer, D. W.: Evaluation of Various Methods of Investigating the Circulation of the Lower Extremities, *Am. J. M. Sc.* **185**:402 (March) 1933.

36. Johnson, C. A.: Studies of Peripheral Vascular Phenomena: I. A New Device for the Study of Peripheral Vascular Phenomena in Health and Disease, *Surg., Gynec. & Obst.* **55**:731 (Dec.) 1932.

mechanism are shown by the variation in form and time of the pulse wave. After the induction of vasodilatation by the local application of heat there is a remarkably constant form to the pulse wave, which is often individual for the same digit in structural disease. The instrument is capable of the demonstration of defects into the digit but gives no indication of the location of the point of stenosis. It does indicate to some extent the presence of collateral circulation.

Observations on skin temperature often closely parallel the findings but show a considerable lag with increases in vasodilatation. The instrument is not subject to all the limitations of observations on skin temperature, particularly in that the cooling of evaporation, air currents and minor changes in environmental temperature have no direct effect. After sympathectomy, when the skin temperature is elevated, the plethysmograph may show very small pulse waves due to increased vascular tone. This occurs late, from two to three weeks afterward, and not after acute interruption of the vasomotor pathway. It is subject to the same emotional and general vasomotor reactions and has the additional advantage that observations may be made on an extremity immediately after exposure to heat or cold by immersion. This should make this method particularly valuable in the diagnosis of disease in the smaller digital arteries.

* *Reaction to Histamine.*—Following the work of Lewis,³⁷ Starr³⁸ and de Takáts³⁹ utilized the cutaneous reaction to histamine as an indication of circulatory efficiency. The latter used an intracutaneous method with the injection of 0.1 cc. of a 1:1,000 solution of histamine with observations on the resulting flare. De Takáts emphasizes the importance of having the extremity in the horizontal position, because the level of the part has a determining effect on the reaction. He found that the results of this test follow the observations on skin temperature fairly closely and can be correlated with the oscillometric findings but give a much better indication of the efficiency of the collateral circulation, which the oscillometer fails to reveal. The intensity of the response to histamine followed the temperature gradient of the extremity when there was organic impairment of the arterial blood flow. With improvement of the circulation as a result of successful treatment, the peripheral extent of the histamine test was reflected in the improvement. The test

37. Lewis, Thomas: *The Blood Vessels of the Human Skin and Their Responses*, London, Shaw & Sons, Ltd., 1927.

38. Starr, Isaac, Jr.: *Change in the Reaction of the Skin to Histamine*, J. A. M. A. **90**:2092 (June 30) 1928.

39. de Takáts, Géza: *The Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities*, Arch. Int. Med. **48**:769 (Nov.) 1931.

was accurate in all cases in which there was evident structural arterial impairment except those in which collateral circulation was adequate and in which circulatory impairment was suggested by the oscillometric readings. De Takáts found that the reaction was modified by vasoconstriction of the small blood vessels of the skin. When vasoconstriction was induced by immersion of the part in cold water there was a failure of normal response. The same reaction occurred in cases of vasospastic disorders, such as Raynaud's disease, and, as Lewis³⁷ previously showed, when the circulation was occluded by application of a cuff for the testing of blood pressure inflated above systolic pressure. The flare appeared, however, when the obstruction was released and blood was admitted to the extremity so that the dilated vessels could be filled. In conjunction with other tests it has proved to be of confirmatory importance in establishing the location of the optimum level of amputation. In short, the test is an indication of the available flow of blood into the vessels of the skin and the state of contraction of these vessels. It is a simple clinical test which may be used to determine the presence of adequacy of the cutaneous collateral circulation and together with the other usual tests affords an estimate of the efficiency of the circulation of the extremities.

Kramer³⁵ found essentially the same relationship between the histamine and the oscillometric test for circulatory efficiency. He decided that a prompt normal reaction indicated a satisfactory circulation, which might be adequate even when some of the deeper vessels were apparently occluded. The wheal and flare should appear within five minutes, and he considers that a delay is evidence of impairment of circulation.

Perlow⁴⁰ advises a test using a 1:2,000 solution of histamine in a 0.5 per cent solution of procaine hydrochloride. The reaction is said to be essentially the same as that of others and when used intradermally is painless.

Release of Vascular Tone.—Measurement of vascular tone has been widely used both for the determination of structural disease and for its differentiation from vasospastic disorders as well as for investigation of the degree of vasospasm imposed by, or occurring in conjunction with, organic obstruction. In addition, it is the principal method by which the success of sympathetic ganglionectomy might be indicated. Measurements of skin temperature are used in general for the measurement of the degree of vasodilatation secured, but plethysmographic methods are at least as accurate.⁴¹

40. Perlow, S.: A Painless Histamine Test: An Experimental Study, *Ann. Int. Med.* **7**:561 (Nov.) 1933.

41. Scupham, G. W., and Johnson, C. A.: Peripheral Vascular Phenomena: III. The Peripheral Pulse Volume in Occlusive Arterial Diseases, *Arch. Int. Med.* **52**:877 (Dec.) 1933.

Peripheral vasodilatation is generally produced by one of three methods in the clinical study of vascular diseases: (1) increased internal production of heat; (2) increased environmental temperature applied locally or generally, and (3) temporary interruption of the vasoconstrictor pathway through the sympathetic nervous system.

Brown⁴² introduced and has used the method of artificial induction of fever by the intravenous injection of typhoid vaccine to secure marked peripheral vasodilatation. The rise in temperature of the distal portions of the extremity in the absence of organic obstruction to the flow of blood increases much more than the increase of body temperature if the initial temperature is sufficiently low. This he has expressed as the vasomotor index, which is calculated by subtracting the increase in oral temperature from the increase in peripheral temperature with the result divided by the increase in oral temperature. Normal values are from 2 to 10. If a temperature of at least 29 C. (84.2 F.) is reached in the skin of the affected digits after fever is induced, satisfactory ability for vasodilatation is assumed to exist. Conversely, if the rise is small, high grade obstruction is present with little or no capacity for vasodilatation. This method is not applicable to ambulatory patients and is contraindicated for those with arteriosclerotic disease, the aged and those debilitated from other causes.

Landis and Gibbon⁴³ were able to secure efficient vasodilatation in the extremities by immersion of the two opposite members in water at a temperature of from 40 to 45 C. for a period of about thirty minutes. Within certain limits they found this method to be sufficiently effective for the usual clinical diagnostic purposes. When the hands were immersed the temperature of the toes rose to 31.5 C. or more in normal persons, which Scott and Morton⁴⁴ regard as the minimum normal rise following general and spinal anesthesia. In the event of organic structural impairment of circulation there was a much more limited rise in the affected extremities comparable to the grade of impairment. In comparison with other methods for the inhibition of vasoconstrictor tone, it was found that in most instances of structural insufficiency this method was equally satisfactory in result and much easier to carry out. In a few cases Landis and Gibson were able to secure evidence of dilatation of the peripheral vessels by artificial fever or nerve block when vasoconstrictor tone could not be completely released

42. Brown, Allen and Mahorner.²⁵ Brown.^{31a}

43. Landis, E. M., and Gibbon, J. H., Jr.: A Simple Method of Producing Vasodilatation in the Lower Extremities with Reference to Its Usefulness in Studies of Peripheral Vascular Diseases, *Arch. Int. Med.* **52**:785 (Nov.) 1933.

44. Scott, W. J. M., and Morton, J. J.: Sympathetic Activity in Certain Diseases, Especially Those of the Peripheral Circulation, *Arch. Int. Med.* **48**: 1065 (Nov.) 1931.

by warming the extremities, and so they advise in case of doubt as to the efficiency of this method that it be checked against other methods. In some cases of Reynaud's disease and acrocyanosis the increased constrictor tone in response to low environmental temperature is so great that release by this method is not obtainable. In such instances it was found that a slow warming of the parts was obtainable by peripheral nerve block. The procedure, then, is particularly useful in the diagnosis of organic disease and in the determination of the amount of vasoconstriction existing in cases of such disease.

Lewis and Pickering¹² had earlier achieved the same result, perhaps securing even a greater degree of vasodilatation by means of a heat cabinet into which the patient was placed with the hands or feet exposed to a room temperature which was maintained at a lower level (from 16 to 18 C.) than that of the cabinet. With the environmental temperature at a low level a greater rise is secured because of the lower initial starting point. Coller and Maddock¹⁰ used a similar method by placing the patient under a rubber blanket and preventing the elimination of heat from the body as well as increasing the environmental temperature. They were able to secure marked vasodilatation.

When the plethysmograph is used for the measurement of vasodilatation the same extremity may be immersed in water at 45 C. and maximum vasodilatation secured.⁴¹ A similar result can be achieved by the method of Landis and Gibbon,⁴³ but when it is followed by direct heating of the extremity an even greater increase in the flow of blood is demonstrable.

The release of vascular tone by temporary interruption of the sympathetic pathways to an extremity was first applied to the differential diagnosis of organic and vasospastic arterial diseases almost at the same time by Morton and Scott,⁴⁵ White⁴⁶ and Brill and Lawrence.⁴⁷ They found that with the administration of spinal anesthesia vasoconstrictor tone to the lower extremities could be completely abolished and a marked rise in surface temperature could be measured. The same effect was produced by general anesthesia, and almost identical levels of peripheral cutaneous temperature could be reached in normal persons by either method and no further increase could then be detected. It was assumed that complete inhibition of vasoconstriction occurred, and that maxi-

45. Morton, J. J., and Scott, W. J. M.: The Measurement of Vasoconstrictor Activity in the Lower Extremities, *J. Clin. Investigation* **9**:235, 1930. Scott, W. J. M., and Morton, J. J.: Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients, *J. A. M. A.* **97**:1212 (Oct. 24) 1931.

46. White, J. C.: Diagnostic Blocking of Sympathetic Nerves to the Extremities with Procaine, *J. A. M. A.* **94**:1381 (May 3) 1930.

47. Brill, S., and Lawrence, L. B.: Changes in Temperature in the Lower Extremities Following the Induction of Spinal Anesthesia, *Proc. Soc. Exper. Biol. & Med.* **27**:728, 1930.

num vasodilatation could be reached with uniformity in different persons.

Lewis and Landis,⁴⁸ White,⁴⁶ Scott and Morton⁴⁴ and others have used the method of peripheral nerve block by local anesthesia for the study and differential diagnosis of vascular diseases.

In the foot, injection into the posterior tibial nerve is easy as it passes behind the internal malleolus at the ankle. In the upper extremity the ulnar nerve at the elbow may be used or the median nerve at the wrist. With complete anesthesia of the cutaneous area corresponding to the distribution of the nerve, the skin temperature in normal persons rises to sufficiently high levels to indicate satisfactory vasodilatation but not quite to that of general or spinal anesthesia.

Scott and Morton⁴⁴ consider this a satisfactory method for estimating vasoconstriction but in borderline cases suggest that it be checked with the patient under spinal or general anesthesia. They have established normal levels for vasodilatation for the first toe at 31.5 C. with the patient under spinal and general anesthesia and at 30.5 C. with posterior tibial nerve block if these procedures are carried out at a room temperature of 20 C.

On the basis of this method Scott and Morton were able to divide circulatory syndromes into three main groups, due to (1) occlusion alone, (2) spasm alone and (3) mixed spasm and occlusion. In the first group there is no significant rise in temperature; in the second there is a rise to approximately the normal level for vasodilatation and in the third the response lies between and is significant in proportion to the degree of rise.

The methods of estimating vasoconstrictor tone, particularly peripheral nerve block, have a wide field of usefulness, but it must be borne in mind that normal vasoconstrictor tone as a response to the heat-regulating mechanism of the body should not be confused with pathologic angiospasm.⁴⁹ Both are no doubt participants in clinical phenomena.

Oxygen Tension of the Blood.—This has been noted particularly in the study of arteriovenous aneurysms and of erythromelalgia. It is particularly important in the former.

Weiss and Ellis⁵⁰ have recently studied the utilization of oxygen and the production of lactic acid by the muscles in the peripheral cir-

48. Lewis, T., and Landis, E. M.: Some Physiological Effects of Sympathetic Ganglionectomy in the Human Being and Its Effect in a Case of Raynaud's Malady, *Heart* **15**:151, 1930.

49. Lewis, Pickering and Rothschild.^{27b} Coller and Maddock.¹⁶

50. Weiss, Soma, and Ellis, L. B.: Oxygen Utilization and Lactic Acid Production in the Extremities During Rest and Exercise in Subjects with Normal and in Those with Diseased Cardiovascular Systems, *Arch. Int. Med.* **55**:665 (April) 1935.

ulation. They found that the degree of loss of oxygen from the arterial blood in relation to the consumption of oxygen of the tissues was one of the best measures of the state of the peripheral circulation. The average level of lactic acid with the patient at rest was likewise found to be uniform in normal persons and in patients with all types of cardiac disease. The utilization of oxygen is normal in persons with cardiac disease also, except in cases of congestive failure. This is due to a reduction in the peripheral circulation.

The more extensive application of these methods to the study of vascular diseases may be of considerable importance.

Arteriography.—In cases of arteriosclerosis visualization of the arteries of the extremities has been of some value in that by its means the presence, and to some extent the degree, of calcification could be determined. No conception can be obtained of the efficiency of the circulation in calcified vessels.⁵¹

With the introduction of a satisfactory opaque solution, considerable progress has been made. Leriche⁵² believes that only one satisfactory agent is available at present, namely, a stable solution of thorium dioxide. While solutions of sodium iodide are satisfactory from a technical standpoint and for the observation of veins, the arterial spasm induced renders them dangerous. He has frequently observed cadaveric pallor in an extremity following its use even with the patient under anesthesia, which is usually necessary because of the severe pain which the intra-arterial injection of this drug often precipitates. With thorium dioxide Leriche has seen no bad results in an extensive experience, and he considers its use in the diagnosis of vascular disease of great value.

A number of reports of accidents in the use of other types of opaque mediums for arteriography have appeared from France.⁵³

Allen and Camp⁵⁴ have described a satisfactory technic for the use of solution of thorium dioxide with good results. The report of Veal

51. Lansbury, J., and Brown, G. E.: The Clinical Significance of Calcification of the Arteries of the Lower Extremities, *Proc. Staff Meet., Mayo Clin.* **9**:49 (Jan. 24) 1934.

52. Leriche, R.: Sur la b nignit  des art riographies au thorotrast, *Bull. et m m. Soc. nat. de chir.* **61**:175 (Feb. 16) 1935.

53. Leven , Jacques: Les dangers de l'art riographie, *Bull. et m m. Soc. nat. de chir.* **61**:6 (Jan. 19) 1935. Bazy, L., and Reboul, H.: Etude critique sur l'art riographie, *ibid* **61**:18 (Jan. 19) 1935.

54. Allen, E. V., and Camp, J. D.: Arteriography: A Roentgenographic Study of the Peripheral Arteries of the Living Subject Following Their Injection with a Radiopaque Substance, *J. A. M. A.* **104**:618 (Feb. 23) 1935; The Value of Arteriography, *Radiology* **22**:678 (June) 1934.

and McFetridge⁵⁵ is essentially the same. The chief value of this method is not for diagnosis only; information is obtained regarding details of circulation in cases of arterial disease not otherwise obtained, particularly in regard to the collateral circulation. In the normal arm and hand the vessels are clearly outlined with a minimum of collateral branches, which in obstructive disease are numerous, particularly in cases of thrombo-angiitis obliterans, in which also the involved arteries usually show a patchy distribution of lesions in various locations, particularly in the palmar and digital arteries of the hand. The contour of the lumen is irregular and varies in size in the initial stages of the disease. The lumen is reduced in size and follows an irregular course, widening and narrowing, often being divided as by an island in a stream. In the final stage complete occlusion of an artery often occurs, with a small channel sometimes extending into an occluded portion.⁵⁶

In arteriosclerosis the extent and degree of the lesions show great variation. The principal arteries and collateral branches are involved. The arterial image loses its curves and regular contours and shows marked tortuosity. The size of the lumen varies and may be thread-like or obliterated. Collateral circulation is conspicuously limited. Segmental obliteration is sometimes seen with the vessel functioning below the point of obstruction.⁵⁷

Information may be gained concerning arteriovenous fistulas, the characteristics of which are dilatation of the arteries leading to the fistula and pooling of the medium in the region of the fistula. Horton⁵⁸ was able to visualize an aneurysm involving the femoral artery and vein and thus establish its definite location. Yater and White⁵⁹ were able to show the exact location, size and shape of an arteriovenous aneurysm of the ulnar artery.

Veal and McFetridge⁵⁵ are of the opinion that in the selection of the location for amputation in a case of gangrene arteriography is of considerable value and is a more reliable indication of adequate collateral circulation than the histamine test.

55. Veal, J. R., and McFetridge, E. M.: Adequate Circulation in the Extremities, *J. A. M. A.* **104**:542 (Feb. 16) 1935; Arteriography in Gangrene of the Extremities by the Use of Thorium Dioxide (Stabilized), *Ann. Surg.* **101**:766, 1935.

56. Knapp, J. C.: Arteriography, *N. Y. State J. Med.* **35**:76 (Jan. 15) 1935.

57. Contiades, X. L., and Nalleau, J.: Results of Arteriography in Diseases of the Arteries and Tumors, *Presse méd.* **42**:1866, 1934.

58. Horton, B. T.: Arteriovenous Fistula Involving the Common Femoral Artery Identified by Arteriography, *Am. J. M. Sc.* **187**:649 (May) 1934.

59. Yater, W. M., and White, C. S.: Roentgenographic Demonstration of an Arteriovenous Aneurysm by Means of Thorotrast, *Am. J. M. Sc.* **186**:493 (Oct.) 1933.

In regard to the dangers involving the use of solution of thorium dioxide, most writers seem to be in agreement. The fact that the metal is not eliminated but remains fixed in the reticulo-endothelial system is recognized. What the delayed effect of the retention of a radioactive substance of this type may be is not known, but until now no harmful effects have been reported.

THROMBO-ANGIITIS OBLITERANS

Although the actual cause of thrombo-angiitis obliterans is still obscure, certain phases of the etiology have been established; so predisposing factors may be considered in a more certain light. The racial factor has been disposed of. The disease has occurred in almost all races. Horton and Brown⁶⁰ have observed 10 cases in women in a total of about 700. In addition to these they reviewed the literature on the few cases previously reported. This seems to illustrate the rarity of the disease in the female, and it is worthy of note that all these cases were relatively mild. These authors believe that the disease occurs in women in so mild a form that it is overlooked because few subjective phenomena present themselves. Silbert⁶¹ found only 2 cases in women in over 2,000 and admits a total of only 9 in women among 2,200 reported in the literature. He finds that the disease occurs more frequently in Jews and notes that it has been reported in brothers more frequently than is accounted for by coincidence. This suggests a hereditary sex-linked factor by which the disease may be transmitted through the female to the male offspring.

In regard to the relationship of tobacco, Silbert and his associates⁶² say that typical examples of thrombo-angiitis obliterans have not occurred in nonsmokers and that sensitiveness to tobacco is one of the primary factors in its cause. Some other workers are of the opinion that tobacco is not primarily concerned as an etiologic factor but that it is important in influencing the progress and severity of the disease.

There can be no question that cigaret smoking particularly plays a most important, if coincidental, rôle in the disease. The initial effect of nicotine on the sympathetic ganglions has long been known, as well

60. (a) Horton, B. T., and Brown, G. E.: Thrombo-Angiitis Obliterans Among Women, *Proc. Staff Meet., Mayo Clin.* **7**:107 (Feb. 24) 1932; (b) Thrombo-Angiitis Obliterans Among Women, *Arch. Int. Med.* **50**:884 (Dec.) 1932.

61. Silbert, Samuel: Thrombo-Angiitis Obliterans in Women: Report of Two Cases, *Ann. Surg.* **101**:324 (Jan.) 1935.

62. Harkavy, J.; Habold, S., and Silbert, S.: Tobacco Sensitiveness in Thrombo-Angiitis Obliterans, *Proc. Soc. Exper. Biol. & Med.* **30**:104 (Oct.) 1932.

as its transient effect on the heart rate and blood pressure. In addition to these, it has been well established that peripheral vasoconstriction occurs in almost all subjects, whether habituated smokers or not, as measured by a decrease in the surface temperature of the extremities.

Maddock and Coller⁶³ in well controlled experiments showed that in addition to the increase of heart rate and rise in blood pressure there was a consistent fall in surface temperature, greatest in the toes, after the smoking of a cigaret. This fall in temperature lasted until after the other cardiovascular phenomena had returned to normal. They are of the opinion that the effect is directly on the sympathetic nervous system, as it failed to occur in a patient with peripheral nerve block and in a patient on whom sympathetic ganglionectomy had previously been carried out. The effects on the heart rate and blood pressure were the same as those in normal persons. The authors believe this to be an effect of small amounts of nicotine. The degree depends on the rapidity of smoking as well as on inhalation. To corroborate this view they were able to obtain a similar effect by the intravenous injection of nicotine in the amount comparable to what might be obtained by the smoking of a cigaret. The results of this experiment were the same as those produced by smoking on heart rate, blood pressure and peripheral surface temperature.

Johnson and Short⁶⁴ think that the main action of smoking is a brief stimulation by nicotine of the sympathetic ganglions, that the rise in blood pressure is by visceral and later peripheral vasoconstriction resulting from stimulation of the adrenal glands through the sympathetic system by nicotine. This is comparable to the rise in blood sugar on smoking noted by Haggard and Greenberg,⁶⁵ which they attributed to an increased rate of discharge of epinephrine resulting from stimulation of the sympathetic ganglions.

That the vascular phenomena accompanying smoking are due to combustion of the tobacco and not to the paper of cigarets is further corroborated by Barker,⁶⁶ who found that the same effects follow smoking by patients with thrombo-angiitis obliterans as occur in normal persons. The conclusions of Wright and Moffat⁶⁷ are in agreement that nicotine is at least one of the important toxic factors and carbon

63. Maddock, W. G., and Coller, F. A.: The Relation of Peripheral Vasoconstriction to Tobacco, *Ann. Surg.* **98**:70 (July) 1933.

64. Johnson, H. J., and Short, J. J.: Effect of Smoking on Skin Temperature, *J. Lab. & Clin. Med.* **19**:962 (June) 1934.

65. Haggard, H. W., and Greenberg, L. A.: The Effects of Cigarette Smoking on Blood Sugar, *Science* **79**:165, 1934.

66. Barker, N. W.: The Vasoconstrictor Effects of Tobacco Smoking, *Proc. Staff Meet., Mayo Clin.* **8**:284 (May 10) 1933.

67. Wright, I. S., and Moffat, D.: The Effects of Tobacco on the Peripheral Vascular System, *J. A. M. A.* **103**:318 (Aug. 4) 1934.

monoxide and the products of paper combustion are not the cause. They found almost the same results with denicotinized cigarettes, the content of which is about 40 per cent of the average of standard brands. In addition to the fall in peripheral cutaneous temperature, they found on observation of the capillaries of the nail fold that there was a marked slowing and even stasis of the blood in these vessels after the smoking of a single cigaret. This effect was variable even in the same person at different times, as are the variations in skin temperature, which are most marked in the periphery and which fail to show any comparable change when readings are made on the forehead.

With the idea that allergy might be a factor in thrombo-angiitis obliterans, Harkavy, Hahold and Silbert⁶² investigated 68 cases and found that in more than 80 per cent there was a reaction to one or more of five tobacco allergens by cutaneous test. Of the control group of 107 patients who were comparable cigaret smokers, 97 gave a negative reaction to all five allergens; 15 of these had atherosclerotic vascular disturbances, and all were heavy cigaret smokers. In 13 of 20 cases passive transfer was accomplished. In their studies Wright and Moffat,⁶⁷ although they found positive cutaneous reactions with tobacco and nicotine, were unable to show any relationship to the fall in surface temperature.

Sulzberger⁶⁸ found a positive reaction of the skin to tobacco in 78 per cent of 24 patients with thrombo-angiitis obliterans, in 36 per cent of smokers without this disease and in only 16 per cent of nonsmokers. He was unable to demonstrate passive transfer except in 1 case. He was able to demonstrate positive cutaneous reactions to other allergens and inhalants. He concludes that thrombo-angiitis obliterans is usually the result of hypersensitization to tobacco but may also result from sensitization to other allergens and that nicotine plays no allergic rôle.

It must be admitted that the high percentage of positive cutaneous reactions to tobacco in patients with thrombo-angiitis obliterans is significant in contrast to that obtained in normal users of tobacco and in nonsmokers, and it is likewise reasonable to believe that if thrombo-angiitis is an allergic vascular reaction primarily, other factors than tobacco may be the offending agents in nonsmokers. This, however, does not explain the great variation in sex incidence. But, be that as it may, there is little reason to doubt the additional part played in the disease by the toxic action of small amounts of nicotine by inhalation in the production of damaging vasoconstriction in anatomically impaired vessels or in a barely sufficient collateral circulation.

68. Sulzberger, M. B.: Recent Immunologic Studies in Hypersensitiveness to Tobacco, J. A. M. A. **102**:11 (Jan. 6) 1934.

Jäger⁶⁹ as a result of his careful pathologic studies of this disease believes that there is a generalized reaction of the intima as the initial lesion; he mentions allergy as well as a specific bacterial or other intoxication as a possible factor which secondarily brings about thrombosis.

Certainly, whatever the primary cause may be, the idea of infection seems unlikely. The innumerable bacteriologic studies of the blood and excised thrombi of vessels have all been fruitless. Buerger⁷⁰ was unable to reproduce the vascular lesion even by the injection of thrombotic material from a patient with migrating phlebitis into the ligated vein of another person. He was able to reproduce a lesion locally by applying the clot so removed under and to the side of a ligated vein with the scrapings of the intima applied to the adventitia. In from ten to twelve days the characteristic histologic changes of thrombo-angiitis obliterans occurred. This is the only evidence of infection.

It has been suggested⁷¹ that trauma, minor infections and exposure to cold to which the extremities are subject are factors which predispose to thrombosis in the peripheral vessels as well as tobacco. Since the visceral vessels are not concerned with the regulation of temperature by conservation of heat and are not subject to the extremes of environmental change, thrombosis does not so readily develop there.

The relationship of this disease to endocrine disturbances has been suggested, and the parathyroid glands, because of the elevation of the calcium content of the blood, have been suspected. Bastai and Dogliotti⁷² performed partial parathyroidectomy in 5 cases with lowering of the calcium content of the blood, immediate cessation of pain and healing of wounds previously resistant to treatment. The significance of this work and that of others remains to be seen.

Pathology.—The pathologic picture presented in the stage of thrombosis or later has been the basis for the opinion that thrombo-angiitis obliterans is an inflammatory disease of infectious origin. The typical pathologic change in the peripheral vessels is so well known that there is no need of repeating the description here.

The most important recent advance in the knowledge of the pathologic process is brought to light in the excellent studies of Jäger.⁶⁹ In

69. Jäger, Ernst: The Pathologic Anatomy of Thrombo-Angiitis Obliterans in Juvenile Gangrene of the Extremities, *Virchows Arch. f. path. Anat.* **284**:526, 1932.

70. Buerger, Leo: Thrombo-Angiitis Obliterans: Experimental Reproduction of the Lesions, *Arch. Path.* **7**:381 (March) 1929.

71. Taube, N.: Mesenteric Involvement in Buerger's Disease, *J. A. M. A.* **96**:1469 (May 2) 1931.

72. Bastai, P., and Dogliotti, G. C.: Hyperparathyroïdie et syndrome angiospastique, *Presse méd.* **42**:1761 (Nov. 10) 1934.

addition to the usual findings he was able to demonstrate a general intimal reaction extending far beyond the location of the active lesions. This he says is the fundamental initial type of lesion. It consists of a cushioning of the intima with the development of nodular raised areas, exudative and proliferative and containing giant cells. These foci are somewhat similar to the Aschoff body of rheumatic fever. In fact, Jäger states that the pathologic process of thrombo-angiitis obliterans in the large arteries resembles that of rheumatic fever; in the medium-sized arteries, that of vegetative endocarditis, and in the small arteries, periarteritis nodosa.

Telford and Stopford⁷³ have recently advanced the theory that the initial lesion in thrombo-angiitis obliterans is intimal proliferation followed by thrombosis and atypical organization in the medium-sized arteries of the legs. They believe that vascular spasm is primary and the intimal changes are the result. They point out that they have found that the thrombosis and fibrosis which involve the perivascular structures extend beyond the intimal proliferation, which may be limited to a very small area.

Morgan⁷⁴ says that the lesion may be present in any of the large arteries or veins and may originate in any part of an artery with or without involvement of the adjacent venae comites. The lesion may begin in a vein without a similar condition in the adjacent artery. The initial lesions begin in one or more isolated areas and later progress from one or more foci to the chronic stage with irregular scattered lesions.

Evidence at autopsy of involvement of visceral arteries in cases of peripheral thrombo-angiitis obliterans has been reported by a number of observers. Taube,⁷⁵ with a report of 2 additional cases, reviews the literature. The diseased vessels included the aorta, the coronary arteries and the mesenteric, renal, spermatic, celiac axis and cerebral arteries, usually in combination. Averbuck and Silbert⁷⁵ reported on the cause of death in 47 cases of typical thrombo-angiitis. There were autopsies in 19. In 22 the patient died of a vascular accident, and in 18, of coronary thrombosis. The authors point out that the findings in the visceral vessels were not always characteristic of the disease; even in a patient aged 24 there was arteriosclerosis of the coronary arteries. The authors are of the opinion that the vascular involvement of the visceral vessels bears a definite relation to the peripheral disease.

73. Telford, E. D., and Stopford, J. S. B.: Thrombo-Angiitis Obliterans, *Brit. M. J.* **1**:863 (April 27) 1935.

74. Morgan, J. R. E.: Distribution of the Lesions of Thrombo-Angiitis Obliterans in the Vessels of the Leg, *Arch. Path.* **18**:216 (Aug.) 1934.

75. Averbuck, S. H., and Silbert, S.: Thrombo-Angiitis Obliterans: The Cause of Death, *Arch. Int. Med.* **54**:436 (Sept.) 1934.

Allen and Willius⁷⁶ reported 7 clinical cases of coronary disease in 225 living patients and are of the opinion that it is not a significant number.

Birnbaum, Prinzmetal and Connor⁷⁷ report a case of generalized vascular disease in which clinically the picture was that of multiple thrombosis involving the mesenteric as well as the peripheral vessels, finally terminating with bilateral adrenal infarction. The pathologic findings, while not typical in all essentials, resembled those of thrombo-angiitis obliterans more nearly than those of any other vascular disease. There was no clinical peripheral arterial involvement, and it was the authors' impression that adrenal infarction caused death before the typical manifestations of the disease became evident.

In a case reported by Telford and Stopford,⁷³ that of a man 26 years of age, the condition terminated in sudden death by coronary thrombosis. The pathologic changes in the coronary arteries were indistinguishable from those of typical thrombo-angiitis obliterans.

In the 5 cases reported by Jäger⁶⁹ the general involvement was typical of the disease, the blood vessels of the brain, heart, kidneys, liver, spleen, stomach and lungs being involved in typical fashion. He concludes that the disease is not limited to the vessels of the extremities but attacks the entire vascular system.

Thus, it seems that extensive visceral involvement does occur at least in a certain number of cases. It is certainly true that these comprise only a small portion of the total number of cases of the disease, and, clinically at least, thrombo-angiitis obliterans must be considered essentially a disease of the peripheral arteries.

Clinical Syndrome.—This has been so completely described by Buerger²³ and others that little has been added. The symptomatology is dependent on the impairment of arterial circulation, migrating phlebitis or their complications. The pain of intermittent claudication is usually the initial symptom, although fatigue in the muscles of the legs and coldness of the extremities with vasospastic symptoms, particularly in the hands, suggesting the Raynaud syndrome are not uncommon. Trophic ulcers, superficial phlebitis or even sudden arterial occlusion may be the presenting symptoms.^{31a} It has been suggested that even though these are the initial symptoms the disease has been progressing for months or years before becoming evident.⁷³

76. Allen, E. V., and Willius, F. A.: Disease of the Coronary Arteries Associated with Thrombo-Angiitis Obliterans of the Extremities, *Ann. Int. Med.* **3**:35, 1929.

77. Birnbaum, W.; Prinzmetal, M., and Connor, C. L.: Generalized Thrombo-Angiitis Obliterans: Report of a Case with Involvement of Retinal Vessels and Suprarenal Infarction, *Arch. Int. Med.* **53**:410 (March) 1934.

The pain which occurs is usually of two types: (1) pain that is induced by exercise or (2) that which occurs while the patient is resting. The former is the well known intermittent claudication usually considered the result of muscular ischemia, rarely of phlebitis.⁷⁸ Pain while the patient is resting may precede ulceration or gangrene. It is continuous, often worse at night and aggravated by change in posture; after gangrene or ulceration appears the deep burning pain may change to superficial burning. Secondary infection may be a dominant factor even to the extent of formation of abscesses.⁷⁹ With phlebitis or arteritis the pain is less severe and is generalized or aching, while with arterial occlusion it is sudden and severe and radiates peripherally. The pain which accompanies ischemic neuritis is severe and diffuse, covering large areas, does not correspond entirely to nerve distribution and is paroxysmal and often lancinating.

Variation in color with change in position has been described previously, and examination by various methods demonstrates impairment of arterial circulation, usually in more than one extremity.⁷³

The general opinion is that this disease runs a chronic course of varying duration and then tends to stop progressing and becomes healed. Collateral circulation is extensive and if it is adequate may restore the extremity to usefulness with a minimum loss of tissue.

Brown^{31a} recognizes five clinical types: 1. In the compensated type the disease is of long duration, trophic changes do not occur, and adequate collateral circulation has developed. Fatigue and mild claudication are the important symptoms. 2. In the slowly progressive type symptoms and signs of arterial occlusion are evident, with pain and reduced surface temperature. Improvement is followed by relapses. The collateral circulation keeps pace fairly well with the occlusive process.

3. Limited areas of gangrene occur with superficial ulcers of the digits, and pain while the patient is at rest occurs during the active stages of ulceration. The collateral circulation is nearly adequate, and no large amount of tissue is lost. The ulcers are induced by trauma, unnecessary surgical intervention or the application of antiseptics.

4. In the acute progressive type there is the picture of extensive arterial occlusion, with rapid development, severe claudication and severe pain while the patient is at rest and the appearance of gangrene and larger ulcers.

78. Goldsmith, Grace A., and Brown, G. E.: Pain in Thrombo-Angiitis Obliterans, Proc. Staff Meet., Mayo Clin. 9:201 (April 4) 1934.

79. Samuels, S. S.: Thrombo-Angiitis Obliterans with Secondary Abscess Formation in the Extremities, M. Rec. 139:116 (Feb. 7) 1934.

5. The extreme type with massive gangrene often occurs as the end-stage of the preceding types. In addition, there are a few distinct variations from this main grouping.

In studies of the capillaries in this disease two general types of reaction of the capillaries have been noted.⁸⁰ There is one in which the capillaries are dilated and the majority are filled and visible. The flow is slow. With dependence of the extremity and the development of cyanosis more of these vessels open, and the flow of blood is still more retarded. In the second type, with phenomena of vasoconstriction, the reaction is similar to that of Raynaud's disease. Constriction of the capillaries is noted, and only a few are visible. The flow is slow and the blood cyanotic. With an increase in temperature there are more vessels to be seen, and the rate of flow increases slightly but is jerky and intermittent. The vessels are not paralyzed, since they respond to epinephrine and histamine locally. Many are actually found to be thrombosed.

Rabinowitch⁸¹ provides an interesting concept of the rôle of the smaller vessels in cases of thrombo-angiitis obliterans. In the early stages of the disease there is increased irritability of the capillaries, so that vasospastic symptoms may be present with rapid changes in capillary tone and symptoms often mistaken for those of the Raynaud syndrome. This would be compatible with the second type of reaction of the capillaries described earlier. In the second stage the vasospastic tendency gives way to a complete loss of capillary tone with dilatation and failure to respond to stimuli corresponding to the first type. The foot or hand is cold, and the color is dusky red. The color depends on the state of dilatation of the cutaneous vessels and not on the rate of blood flow through them. The lowered surface temperature is due to the occlusion of the larger arteries by thrombosis. In the third stage of impairment of the capillaries stasis and thrombosis occur. Gangrene, the author thinks, does not often affect a large area at one time as it does in arteriosclerosis. Small areas of necrosis occur as a superficial ulcer or ecchymotic spot which may gradually spread to involve a whole toe. At the same time similar areas form elsewhere in the adjacent tissue, and the process then gradually spreads until larger areas may be involved.

The cause of these alterations in the capillaries is explained on a metabolic basis. Lecithin is mobilized from the tissues to the blood with the retention of degradation products, such as choline and its derivatives. This is responsible for the lesions of the capillary beds and the thrombotic tendency. The urine of patients contained choline in most

80. Wright and Duryee.³ Brown, Allen and Mahorner.²³

81. Rabinowitch, I. M.: Newer Concepts on the Physiopathology and Treatment of Thrombo-Angiitis Obliterans, *Am. J. Surg.* **21**:260 (Aug.) 1933.

instances in considerable quantity, while the urine of controls did not. There is an increase in the lecithin content of the blood, which may account for the tendency to coagulation.

The abnormal deprivation of the tissues of lecithin is probably also responsible for the absorption of myelin which has been noted by Brown, Allen and Mahorner.²⁵ This has a bearing on the increased irritability of sensory nerves in the part affected and is the explanation offered for the severe intractable pain in the pregangrenous and gangrenous stages of the disease.

In their studies on the chemistry of the blood Friedlander and Silbert⁸² make no mention of lecithin. They did find the values for cholesterol elevated consistently, as were those for total ash, total protein and calcium, while the values for the chlorides and sugar were normal. Decreased blood volume⁸³ and a low basal metabolic rate⁸⁴ have also been recorded. Koukine⁸⁵ reports the viscosity and coagulation time of the blood to be increased and the number of thrombocytes decreased, which is not in accord with the observations of others. There is so little agreement, however, in regard to alteration of the chemical composition of the blood²⁵ in cases of thrombo-angiitis obliterans that the only conclusion that can be drawn in regard to these findings is that they are variable.

It is agreed that arteriosclerosis is frequently found in association with thrombo-angiitis obliterans,⁸⁶ even in relatively young patients. This offers some difficulty in diagnosis in the cases in the older age groups. The increased element of vascular spasm has been pointed to as a distinguishing feature, and also the much greater collateral circulation in thrombo-angiitis obliterans. The presence of arteriosclerosis in other vessels and the demonstration of the presence of calcification by roentgen examination, while not conclusive,⁵¹ are of importance.

In reporting on the occurrence of diabetes as a complication in 4 cases of thrombo-angiitis obliterans, Horton and Allan⁸⁷ comment on the rarity of the association of these two disorders in contrast to the

82. Friedlander, Mae, and Silbert, S.: Thrombo-Angiitis Obliterans (Buerger): VI. Chemistry of the Blood, *Arch. Int. Med.* **48**:500 (Sept.) 1931.

83. Silbert, S.; Kornzweig, A. L., and Friedlander, M.: Studies in Thrombo-Angiitis Obliterans, *M. Rec.* **97**:430, 1920.

84. Silbert, S., and Friedlander, M.: Studies in Thrombo-Angiitis Obliterans (Buerger): Basal Metabolism, *J. A. M. A.* **96**:1857 (May 30) 1931.

85. Koukine, N.: Problems of the Etiology, Clinical Findings and Treatment in Endarteritis Obliterans, *Rev. de chir.* **53**:639, 1934.

86. Barron, M. E., and Lilienthal, H.: Thrombo-Angiitis Obliterans: General Distribution of the Disease, *Arch. Surg.* **19**:735 (Oct.) 1929. Averbuck and Silbert.⁷⁵

87. Horton, B. T., and Allan, F. N.: Thrombo-Angiitis Obliterans in Patients with Diabetes, *Ann. Int. Med.* **7**:799 (Jan.) 1934.

relationship of diabetes to arteriosclerosis. It is interesting to note that in these cases the disease did not seem to be accentuated by the presence of diabetes.

ESSENTIAL THROMBOPHILIA

Nygaard and Brown⁸⁸ reported 5 cases in which thrombosis occurred in cyclic phases. Both arteries and veins were involved, with a widespread distribution of lesions. The cerebral, retinal and other visceral arteries as well as the arteries of the extremities were involved. The veins in which thrombosis developed were mainly those of the lower extremities. The clinical course was stormy, and death from vascular occlusion occurred in 2 cases. The onset was abrupt in apparently healthy persons.

The pathologic changes consisted of a nonreactive type of thrombosis with occasionally a slight reaction in the arterial wall. There was no evidence of arteriosclerosis in the walls of the vessels, nor could the pathologic picture be identified with that of thrombo-angiitis obliterans.

One characteristic was outstanding in all the cases. During the thrombosing phase of the disease and for a considerable period afterward there was a definite increase in the coagulation of the plasma. There were no consistent variations in the albumin-globulin ratio or in the platelet counts. In 50 cases of thrombo-angiitis obliterans and arteriosclerosis with occlusion there were no deviations from the normal in respect to these three tests.

As the authors suggest, cases of this type of what they believe to be a distinct clinical entity are most likely to be considered cases of thrombo-angiitis obliterans. This type of disorder might account for some of the unexplained cases of venous thrombosis as well as of visceral thrombosis in the absence of infection or of degenerative vascular disease.

ARTERIOSCLEROSIS

The term arteriosclerosis is used to include all types of degenerative arterial disease. It is becoming a generally accepted idea that this condition represents a disease process to which older persons are usually most susceptible. Under certain conditions, particularly in cases of diabetes, an identical type of arterial disease occurs in young persons. Its manifestations vary in different persons as well as in different locations in the body.

The whole subject is so well covered in a publication edited by Cowdry⁸⁹ that it is useless to attempt more than the briefest discus-

88. Nygaard, K. K., and Brown, G. E.: Essential Thrombophilia (Thrombosing Disease), Proc. Staff Meet., Mayo Clin. **10**:13 (Jan. 2) 1935.

89. Cowdry, E. V.: Arteriosclerosis: A Survey of the Problem, New York, The Macmillan Company, 1933.

sion here. The relationship of cholesterol to atherosclerosis is reviewed in detail by Anitschkov in Cowdry's volume. In regard to his comparison of observations on the experimental production of atherosclerosis in the rabbit, with his observations on the disease in man, Leary⁹⁰ draws the following conclusions from the study of the coronary arteries: Atherosclerosis is a disease and not the consequence of age, since it appears in the young and is selective in location. The characteristic lesion in youth is fibrosis associated with the presence of lipoid cells which do not appear in large numbers because of the reaction of the fibrous tissue. Thrombosis occurs when there is necrosis which reaches the endothelium from the subendothelial layer. The characteristic lesion in older persons is the accumulation of large collections of lipoid cells with little connective tissue support. As a result of poor nutrition necrosis occurs and so-called atheromatous abscesses develop. The process is primary in the intima. Stresses favor the location of lesions in the elastica and secondarily in the media. The disease can be reproduced by feeding cholesterol to rabbits. The fibrosis which is characteristic of the coronary lesions in young persons is the characteristic cholesterol atherosclerosis of young rabbits. Fibrosis is the reaction of youth, not of species.

Leary⁹⁰ is of the opinion that atherosclerosis is a disease of cholesterol metabolism comparable to diabetes. He is in agreement with Anitschkow⁹¹ that the thyroid gland seems to control in some way the experimental production of atherosclerosis.

Rabinowitch,⁹² in a study of the question in diabetes, was led to believe that excess cholesterol in the blood is an important etiologic factor in the production of arteriosclerosis in the young person with diabetes. He is in agreement with Leary,⁹⁰ Joslin⁹³ and others that diets high in fat promote the early development of arteriosclerosis and concludes that treatment with a diet high in carbohydrate and low in calories has delayed the development of cardiovascular disease in the cases investigated.

The intimal types of arteriosclerosis, whether essentially atherosclerotic or fibrotic, would seem, then, to have the same causative background, and according to Leary⁹⁰ to be merely the difference in response to age. Several other factors of importance should be mentioned, among them the location of the disease process and the type

90. Leary, T.: Experimental Atherosclerosis in the Rabbit Compared with Human (Coronary Atherosclerosis), *Arch. Path.* **17**:453 (April) 1934.

91. Anitschkow, N.: Experimental Arteriosclerosis in Animals, in Cowdry,⁸⁹ p. 271.

92. Rabinowitch, I. M.: Arteriosclerosis in Diabetes: I. The Relation Between Plasma Cholesterol and Arteriosclerosis; II. Effects of the High Carbohydrate Low Caloric Diet, *Ann. Int. Med.* **8**:1436 (May) 1935.

93. Joslin, E. P.: Fat and the Diabetic, *New England J. Med.* **209**:519, 1933.

of vessel involved.⁹⁴ In the large arteries of the elastic type, including the aorta and the main branches, the intimal type of lesion is the only type essentially atheromatous or fibrotic, with lipoid-containing cells. In the large muscular arteries of the extremities, including the radial and ulnar artery and those of the leg, the picture is variable.

It is here that the Mönckeberg sclerosis⁹⁴ is characteristic. It is a primary involvement of the media with necrosis and calcification and is usually considered to be unassociated with the intimal type of arteriosclerosis, although the two conditions may occur simultaneously. The arteries are converted into solid tubes with calcareous material deposited in ring-shaped masses, producing the characteristic goose-neck arteries. This type of disease is associated in pathologic appearance with that produced by the repeated intravenous injection of epinephrine in rabbits. This is in contrast to the intimal atherosclerotic type resulting from feeding of cholesterol. The Mönckeberg type of sclerosis has little effect on the efficiency of circulation. It is in the intimal type that impairment occurs.

In cases of arteriosclerotic gangrene the arteries of the lower extremities show advanced sclerosis with progressive obliteration of the lumen.⁸⁹ The intima shows thickening by the development of collagenous fibrous tissue. This thickening is irregular, and the narrowed lumen may be situated eccentrically. In the deeper layers of the intima there are areas of fatty degeneration and necrosis with the deposits of cholesterol crystals. The process may extend into the media or even to the adventitia, which may be fibrosed. The arteries become extensively calcified with deposits of calcareous material at the line of the intima and media. When the process invades the endothelial layer of the intima thrombosis occurs, which finally brings about complete occlusion of the vessel.

In cases of diabetes the problem is similar except that arteriosclerosis usually becomes evident at a much earlier age. Rabinowitch⁹⁵ states that five years is the usual time necessary for its development, regardless of age. He quotes Shields-Warren and Joslin in regard to the frequency of this condition in children with diabetes. Arteriosclerosis is appreciably affecting mortality. The severity of the diabetes is not connected, and most "vascular deaths" in cases of diabetes result from cardiac disease or gangrene of the extremities. By means of a combined method of examination the incidence of arteriosclerosis in 500 diabetic persons was estimated as 62.6 per cent, a much greater incidence than that obtained by single methods of examination and

94. Ophüls, William: *The Pathogenesis of Arteriosclerosis*, in Cowdry,⁸⁹ p. 249.

95. Rabinowitch, I. M.; Ritchie, W. L., and McKee, S. H.: *A Statistical Evaluation of Different Methods for the Detection of Arteriosclerosis in Diabetes Mellitus*, *Ann. Int. Med.* 7:1478 (June) 1934. Rabinowitch.⁹²

corresponding more nearly to the observations at autopsy. The combined method for the detection of vascular sclerosis was: (1) clinical examination, including the findings of cardiac enlargement, accentuation of the aortic second sound, hypertension and thickening of the vessels; (2) examination of the fundi for sclerosis; (3) roentgen examination of the heart, and (4) examination of the extremities for calcification of the peripheral vessels.

The so-called hyperplastic or diffuse type of arteriosclerosis, which involves primarily the smaller arterial branches and the arterioles, is somewhat confusing. It has been described as endothelial proliferation with hyaline degeneration and, later, fibrosis. The process may readily go on to complete occlusion. It is usually associated with hypertension and is said to occur infrequently in the muscular arterioles.⁹⁶

Graham⁹⁷ states that in the smaller branches of the arteries of the extremities intimal thickening occurs primarily with fibrosis in the so-called senile type of arteriosclerosis. It produces partial occlusion or obliteration of the distal smaller branches. Atrophy of the skin and muscles follows as a result of impairment of their nutrition by these vascular changes.

With such impairment of circulation in the smaller vessels repeated minimal traumas are emphasized as the factors appearing to be the cause of the local development of gangrene involving one or more toes or a small part of the foot. If the trauma is more severe or if infection takes place, thrombosis of the partially occluded arteries follows, and more extensive gangrene is the result.

With the occlusion of a large artery the distal parts become pale or cyanosed, and a large area of gangrene is the result.

Because of the impairment in the smaller arterial branches, collateral circulation is usually poor. In this respect the occlusion in cases of arteriosclerosis differs from that in cases of thrombo-angiitis obliterans and in cases of diabetic arteriosclerosis in younger persons, in whom the obliterating process involves the larger main vessels, leaving the smaller arteries intact for the establishment of collateral circulation. This is not true of diabetic arteriosclerosis developing in older persons who already have well developed arteriosclerosis.

Reid²² comments on these facts and points out that many persons have marked obliterating arteriosclerosis with absence of pulsations and loss of heat who get along well with a narrow margin of safety unless as a result of exposure to cold, injury, infection or sudden arterial occlusion the circulation becomes totally inadequate and gangrene

96. Bell, E. T.: Arteriosclerosis of the Abdominal Viscera and Extremities, in Cowdry,⁸⁹ p. 473.

97. Graham, D.: Chronic Arterial Occlusion of the Extremities, *Ann. Int. Med.* 7:431 (Oct.) 1933.

results. He emphasizes three important facts: 1. Cold, injury and infection often produce demands with which a reduced circulation cannot cope. 2. Gradual occlusion of the peripheral vessels may not show symptoms, while sudden or rapid occlusion, often accompanied by vasospasm, leads to gangrene. 3. An affected extremity may show by tests a better circulation than a symptomless one.

The clinical phenomena are those dependent on circulatory impairment. In addition to nutritional changes in the skin and muscles with atrophy or impairment of the tissues, there are often increasing intolerance to cold, acroparesthesia, fatigue and aching pains with exercise. Cramping pains at night are more common than typical intermittent claudication which occurs less frequently in cases of arteriosclerosis than in cases of thrombo-angiitis obliterans, probably because the larger vessels are not closed and the obliterating process is in the smaller branches.⁹⁷

The same methods of investigation and diagnosis are applicable as in other types of obstructive disease. The vasospastic phenomena are seldom met. Definite information as to calcification of the peripheral arteries may be gained by roentgen examination. Lansbury and Brown⁵¹ found calcified vessels in 65 per cent of men and 28 per cent of women more than 50 years of age. The presence of calcification furnished no information as to the state of the circulation. They concluded that roentgen study is of limited value in distinguishing cases of thrombo-angiitis obliterans from those of arteriosclerosis obliterans.

In regard to the histamine test, Starr⁹⁸ has found that in addition to its diagnostic value in cases of arterial occlusion special significance may be placed on it in cases of diabetes from the standpoint of prognosis. Of the patients in the group studied, none having a normal reaction to the histamine test showed any circulatory disturbance of the feet after a period of five years. Of 32 patients in whom the reaction was impaired, only 5 survived the five year period without serious disturbance. Starr concludes that by means of the test and physical examination persons with diabetes can be divided into three groups: (1) those not threatened with peripheral vascular disease, (2) those in an intermediate group and (3) those in whom extraordinary precautions must be taken to prevent the development of serious disturbance in the feet.

ARTERIAL EMBOLISM

Sudden acute arterial occlusion in the peripheral arteries produces such a clearcut clinical syndrome that there is little difficulty in its recognition. Embolism is the usual cause. The embolus is usually

98. Starr, I., Jr.: The Value of the Cutaneous Histamine Reaction in the Prognosis of Pedal Lesions in Diabetes Mellitus, *Am. J. M. Sc.* **188**:538 (Oct.) 1934.

released from a thrombus in the left ventricle. Rheumatic cardiac disease⁹⁹ and bacterial endocarditis are frequent antecedents. Auricular fibrillation is often present, and embolism may occur with the restoration of a normal mechanism.¹⁰⁰ Rarely, a thrombus in one of the larger arteries may be the source. Paradoxical embolism may occasionally occur.

Pearse¹⁰¹ briefly describes the condition. He states that almost without exception embolism occurs at the bifurcation of a vessel or at the origin of one of its larger branches.

Pain is the outstanding symptom. It is extremely severe, is sudden in onset and starts at the site of the embolism but soon involves the entire extremity distally. Occasionally the pain may be late and become intense one or even two hours after the onset. It is rarely mild or absent.

Locally, the characteristic findings are pallor, decreased cutaneous sensitivity, loss of heat, reduction or absence of reflexes and paralysis. The changes of color are variable. At first the skin is waxy or cadaveric. This pallor gradually shifts to dark blue cyanosis in the distal part, while the proximal surface presents a blotchy discoloration. In the later stages the hand or foot may become shrunken. In some instances, when the collateral circulation is good there may be few changes in appearance, and spontaneous recovery has been reported even when some superficial gangrene has occurred.¹⁰⁰ On the other hand, the extension of thrombosis above or below the point of embolism may result in extensive impairment of circulation.¹⁰²

Allen and McLean¹⁰³ believe that the profound ischemia which follows sudden arterial occlusion is far too marked to be explained by the obstruction of the lumen by the embolus alone. The phenomena which follow are explainable by the theory that widespread arterial spasm occurs involving the occluded vessel and its branches. They quote Seifert, who observed arterial spasm at embolectomy and who concluded that the pain was due to extensive arterial spasm. This view, they state, is also in accord with the experimental work of Gosset, Bertrand and Patel as well as with that of Mulvihill and Harvey.

99. Weiss, Soma, and Davis, D.: Rheumatic Heart Disease: Embolic Manifestations, *Am. Heart J.* **9**:45 (Oct.) 1933.

100. Brust, R. W.: Embolism of the Peripheral Arteries, *J. A. M. A.* **102**: 2172 (June 30) 1934.

101. Pearse, H. E., Jr.: Embolectomy for Arterial Embolism of the Extremities, *Ann. Surg.* **98**:17 (July) 1933.

102. Danzis, M.: Arterial Embolism, *Ann. Surg.* **98**:422 (Sept.) 1933.

103. Allen, E. V., and McLean, A. R.: Treatment of Sudden Arterial Occlusion with Papaverine Hydrochloride: Report of a Case, *Proc. Staff Meet., Mayo Clin.* **10**:216 (April 3) 1931.

SPECIFIC AND NONSPECIFIC TYPES OF ARTERITIS

De Takáts¹⁰⁴ comments on the confusion of the various types of vascular reactions caused by specific agents which are often confused with thrombo-angiitis obliterans. He is of the opinion that this disease picture will eventually be divided into several types of specific disease etiologically. Endothelial proliferative reactions are similar in a variety of conditions and are characterized histologically by cushions of cellular masses which accumulate beneath the endothelium, alter the permeability of the wall of the vessel and are responsible for other changes, such as medial edema, perivascular reactions, thrombosis and even perineuritis. This vascular response is typical of many types of damage, including frost-bite, reaction to electrical discharges and chemical injuries as well as bacterial and allergic reactions. He refers in this view to the work of both Gruber¹⁰⁵ and Hellmuth.¹⁰⁶

Mathieu, Colleson and Chaltus¹⁰⁷ have recently reported 6 cases of arteritis in association with gout. Acute arteritis of the extremities has been reported during the course of typhoid, influenza, cholera, scarlet fever and rheumatic fever.²² Reid states that tuberculosis of the peripheral arteries is rare. The arteries may become involved by direct extension from a nearby lesion or more rarely by infected emboli. Tuberculosis occurs more frequently in the visceral vessels. One case of gangrene of an extremity was reported by Bäumlér which was caused by tuberculosis of the peripheral arteries.

Baumgarten and Cantor¹⁰⁸ in reporting a case of tuberculous mesarteritis with aneurysm of the femoral artery make the statement that tuberculous arteritis as a result of direct extension from a tuberculous process to the small arteries of an organ has no clinical importance other than that of involvement of the organ. It is merely part of the general disease, and involvement of the walls of the vessels under these conditions is of no special importance regardless of the location.

The involvement of large or medium-sized arteries is a rare but important type of vascular disease, as the media is usually involved and aneurysm is the result. Baumgarten and Cantor found only 20 cases reported previously. Their case is the fifth in which arteritis

104. de Takáts, Géza: *Peripheral Vascular Disease*, J. A. M. A. **104**:1463 (April 27) 1935. de Takáts and Mackenzie.^{26a}

105. Gruber, G. B.: *Endarteritis obliterans und Kältebrand*, Beitr. z. path. Anat. u. z. allg. Path. **84**:155, 1930.

106. Hellmuth, Margot: *Ueber Gefässveränderungen bei der Frostgangrän*, Arch. f. klin. Chir. **158**:702, 1930.

107. Mathieu, L.; Colleson, L., and Chaltus, R.: *Gouty Arteritis Obliterans*, Ann. de med. **35**:124 (Feb.) 1934.

108. Baumgarten, E. C., and Cantor, M. O.: *Tuberculous Mesarteritis with Aneurysm of the Femoral Artery: Report of a Case*, J. A. M. A. **100**:1918 (June 17) 1933.

was the result of transmission of the tubercle bacilli through the vasa vasorum into the media of the wall of the vessel. Of these 5, the femoral artery was involved in 4.

Barnard¹⁰⁹ in a recent contribution makes similar comment concerning the frequency of involvement by direct extension to the wall of a vessel from without and its infrequent occurrence by other routes. In the case which he describes the internal carotid and coronary arteries were involved. There was no evidence of spread from adjacent foci. The intima showed hypertrophy and edema, but the media was principally involved by infiltration by granulation tissue consisting of epithelioid cells, lymphocytes, plasma cells, fibroblasts and giant cells. In this granulation tissue were areas of necrosis of varying size. The muscle tissue of the media was largely destroyed in the areas involved. The patient died of cardiac disease.

In regard to the effect of syphilis on the peripheral vessels there has been some variation of opinion. Cerebral syphilitic vascular disease is well recognized, and no comment is needed as to the part of this disease in the large arteries. That it does attack the medium-sized and smaller muscular arteries there can be little doubt. Hermann¹¹⁰ in an excellent paper on this subject comments on the difficulty of decision as to the etiology of vascular disease in the presence of syphilis because even adequate treatment may have little or no effect in the restoration of an already impaired circulation. He gives Warthin's descriptions of the involvement of the smaller arteries. The lesion may appear as panarteritis, periarteritis or proliferating endarteritis. Small arteries showing proliferating and obliterating endarteritis often show extensive perivascular collections of plasma cells, and in these exudates the organism has been demonstrated. There is often secondary degeneration of the intima with fibrosis which develops slowly, usually as a result of impairment of nutrition resulting from involvement of the vasa vasorum in vessels of this class as well as in the aorta. Arteriosclerosis and the syphilitic process are so closely associated in many cases that differentiation is impossible.

Clinically Hermann describes three distinct types of the disease: In the first, angiospastic phenomena are predominant. He thinks that chronic irritation of the perivascular nerve plexuses gives rise to these reflex vasomotor disturbances, which take the form of chronic vasospasm of the peripheral arterioles. The angiospasm disappears with treatment, but whatever organic impairment exists before is unimproved. The second is the endarteritic type, in which the essential lesion is panarteritis or proliferating endarteritis involving the arterioles.

109. Barnard, W. G.: Tuberculous Arteritis, *J. Path. & Bact.* **40**:433 (May) 1935.

110. Hermann, L. G.: Syphilitic Endarteritis, *Am. J. Syphilis* **17**:305, 1933.

It is the most common form of syphilitic arteritis. Active antisyphilitic treatment will usually arrest the progress of the inflammatory disease, but restoration of circulation does not follow. The spontaneous development of an efficient collateral circulation is one of the characteristic features of this type of the disease. It is often adequate for the maintenance of integrity of the tissue, but not always for unlimited function.

The third type is the thrombo-arteritic, characterized by thrombosis of the medium-sized and smaller vessels. This is rather an uncommon type of lesion with syphilis. The symptoms in the case reported by Hermann were similar to those often encountered in cases of thromboangiitis obliterans, with pain the predominant complaint. The main arteries of the lower extremities were occluded, but a fairly effective collateral circulation was present. Marked improvement followed antisyphilitic treatment, and collateral circulation was further benefited by positive and negative pressure treatment.

It should be noted that in all three types of syphilitic disease of the peripheral vessels a spontaneous collateral circulation is one of the outstanding features.

Derick and Hass ¹¹¹ in a recent article describe a case of widespread chronic inflammatory arteritis which they ascribe to syphilis. The small arteries were involved exclusively, and the inflammatory process involved all three coats of the vessels. The arteries were occluded often by proliferative endarteritis or by thrombosis, usually both. Infarction took place in the viscera, where the lesions were extensive and had apparently developed. The relationship of syphilis to the etiology of this case is not conclusive.

Types of arteritis appear occasionally which are reported as atypical. This has been particularly true in some of the reports of cases of periarteritis nodosa.

Barker and Brown ¹¹² report an unusual case of progressive disseminated obliterating arteritis which they were unable to classify. Some of the clinical phenomena were suggestive of periarteritis nodosa, but the pathologic picture was not compatible. The findings were simple endothelial proliferation of the type of obliterating endarteritis which has been described as nonspecific and resulting from a variety of causes. The extraordinary feature of this case was the clinical course, which the authors summarize. The initial symptoms were those characteristic of a typical Raynaud syndrome involving the hands, and they were treated successfully by sympathectomy. Six months later chills and fever developed, which continued irregularly for five months,

111. Derick, C. L., and Hass, G. M.: Diffuse Arteritis of Syphilitic Origin, *Am. J. Path.* **11**:291 (March) 1935.

112. Barker, N. W., and Brown, G. E.: Progressive Disseminating Obliterating Arteritis of Unknown Origin, *M. Clin. North America* **16**:1313 (May) 1933.

until death occurred. Neuronitis occurred in all four extremities, with some evidence of additional cerebral involvement. There were scattered digital and cutaneous vascular lesions with infarction. Diarrhea and abdominal cramps with blood in the stools occurred in episodes, as well as renal involvement.

Horton, Magath and Brown¹¹³ report 2 cases of arteritis of the temporal vessels with similar clinical and pathologic pictures. Localized periarteritis and arteritis were demonstrable and seemed to be identical in the 2 cases. Relapses and remissions occurred in each. Recovery took place finally. Cultures of the excised vessels and pathologic studies failed to reveal a cause. The similarity of the pathologic findings in these cases as well as the similar course suggested a definite disease type which the authors think might be sufficiently characteristic to represent a disease entity, although they have not found corresponding reports in the literature.

Periarteritis nodosa has been considered a rare disease. Haining and Kimball¹¹⁴ report a case to be added to the 150 previously reported, 20 of which these authors say are in the American literature. The disease is seldom diagnosed clinically, and it must be frequently overlooked since its phenomena in fatal cases may often be cardiac or renal and are classified as cardiac or renal disease. Although it is usually considered to be fatal, apparently some patients survive the acute stage. One of Arkin's¹¹⁵ patients lived for four years after the acute attack, and the disease process was then found to be healed on histologic examination.

Periarteritis nodosa is an arterial disease¹¹⁴ involving the medium-sized vessels and often their smaller branches. Secondary changes in the structure supplied occur as a result of circulatory impairment.

The typical gross pathologic change¹¹⁶ is the distribution of multiple nodules scattered along the course of vessels. These nodules are inflammatory or aneurysmal. Occasionally they may be seen in the skin.

There is usually periarterial infiltration consisting for the most part of lymphocytes, polymorphonuclear leukocytes and often eosinophils. Fibrosis occurs in the adventitia and proliferation of the endothelium of the intima, which may result in occlusion of the vessel, in some

113. Horton, B. T.; Magath, T. B., and Brown, G. E.: Arteritis of the Temporal Vessels: A Previously Undescribed Form, *Arch. Int. Med.* **53**:400 (March) 1934.

114. Haining, R. B., and Kimball, T. S.: Polyarteritis Nodosa, *Am. J. Path.* **10**:349 (May) 1935.

115. Arkin, A.: Clinical and Pathological Study of Periarteritis Nodosa: Report of Five Cases One Histologically Healed, *Am. J. Path.* **6**:401, 1930.

116. Curtis, A. C., and Coffey, R. M.: Periarteritis Nodosa: A Brief Review of the Literature and Report of a Case, *Ann. Int. Med.* **7**:1345 (May) 1934.

instances by thrombosis. The media may show necrosis. This process gives rise to the aneurysmal dilatation and nodules on the walls of the vessels which characterize the disease. In some instances this feature may not be present.

In contrast to the findings in cases of thrombo-angiitis obliterans, the visceral arteries are essentially involved, while those of the periphery are involved uncommonly. According to Arkin,¹¹⁵ the organs most frequently involved are the kidneys, heart, liver and gastro-intestinal tract; the muscles, peripheral nerves and central nervous system are less frequently involved. That the disease is capable of producing occlusion of the peripheral arteries is evident by the 3 cases reported by Barnard and Burbury,¹¹⁷ in which gangrene of the fingers and toes occurred. In Carr's¹¹⁸ case the onset was in the lower extremities with the rather early development of gangrene. Apparently this is exceptional.

Arkin¹¹⁵ divides the disease into four stages: (1) the alterative degenerative or beginning stage, (2) the acute exudative inflammatory stage, (3) the stage of granulation or healing and (4) the stage of fibrotic scar tissue or end-stage.

The etiology is unknown.¹¹⁶ The condition has been generally assumed to be of infectious origin, and the association with rheumatic fever¹¹⁹ has been repeatedly noted. Friedberg and Gross¹²⁰ reported 4 cases in which the characteristic pathologic changes of periarteritis nodosa were present in addition to Aschoff bodies in the myocardium. In 1 of these cases there was also malignant nephrosclerosis. The disease occurred in 2 children following scarlet fever. There was no previous history of rheumatic disease. In 1 case in an adult there was a long-standing history of rheumatic fever, and in another only repeated attacks of tonsillitis and sore throat. The relation of this disease to allergy has also been suggested.¹²¹ Mainzer and Joel¹²² describe a typical case associated with sepsis lenta.

The clinical course is variable. It may be sudden in onset and violent and short in duration or insidious in onset, pursuing a subacute

117. Barnard, W. G., and Burbury, W. M.: Gangrene of Fingers and Toes in Case of Polyarteritis Nodosa, *J. Path. & Bact.* **39**:285 (Sept.) 1934.

118. Carr, J. G.: Periarteritis Nodosa, *M. Clin. North America* **13**:1121, 1930.

119. Neale, A. V., and Whitfield, A. G. W.: Rheumatism and Its Relation to Periarteritis Nodosa, *Brit. M. J.* **2**:104 (July 21) 1934.

120. Friedberg, C. K., and Gross, L.: Periarteritis Nodosa: (Necrotizing Arteritis) Associated with Rheumatic Heart Disease, *Arch. Int. Med.* **54**:170 (Aug.) 1934.

121. Masugi, M., and Sato, Y.: Periarteritis Nodosa Allergic Tissue Reactions in the Kidneys: Experimental Study on Pathogenesis, *Tr. Soc. path. jap.* **23**:857, 1933.

122. Mainzer, F., and Joel, W.: Periarteritis Nodosa als Ausdruck einer Sepsis Lenta (*streptococcus viridans*), *Tr. Soc. path. jap.* **23**:857, 1933.

prolonged course with variation in the presenting symptoms. These may be referable to only one organ or to one or more successively, thus reflecting the "hidden vascular insults."¹¹⁴ The clinical manifestations are bizarre. Painful, tender muscles in association with cardiac, renal and abdominal symptoms may occur. Hematuria seems to occur in a majority of the cases at one time or another. The hemorrhage may be massive.¹²³ When the mesenteric vessels are involved there may be severe abdominal symptoms simulating an acute surgical emergency.¹¹⁹ The continued fever with the picture of sepsis or infection associated with anemia and leukocytosis, sometimes with eosinophilia, seems to be fairly constant.

While the diagnosis¹²⁴ is seldom made ante mortem, the multiplicity of symptoms and findings may offer a suggestion, and if the possibility of this disease is kept in mind it would seem that the diagnosis should be more often correctly made. Certainly it seems to have been reported with increasing frequency in the past year or two.

RAYNAUD'S DISEASE

The conception of Raynaud's disease, originally described as a vasomotor neurosis, has been generally accepted until recently. Raynaud's description of the disorder stands, and clinically few important additions have been made in the description of its symptomatology and clinical course. Newer methods of investigation of vascular diseases have led to a better understanding of it and to more certain diagnosis. It must be admitted that errors in diagnosis have been and are frequent. This disease has often been mistaken for thrombo-angiitis obliterans because of the vasospastic phenomena frequently present.¹²⁵ Reactions to cold occasionally simulate the Raynaud paroxysm in this disorder. It has been described in cases of scleroderma, paroxysmal hemoglobinuria,¹²⁶ chronic arthritis,¹²⁷ tuberculosis¹²⁸ and other diseases. It would seem that this

123. Wever, G. K., and Perry, Isabella: Periarthritis Nodosa: Report of a Case with Fatal Perirenal Hemorrhage, *J. A. M. A.* **104**:1390 (April 20) 1935.

124. Grill, C.: Ein Beitrag zur Diagnose und Prognose der Periarthritis Nodosa, *Acta med. Scandinav. (supp.)* **59**:634, 1934.

125. (a) Allen, E. V., and Brown, G. E.: Raynaud's Disease: A Clinical Study of 147 Cases,, *J. A. M. A.* **99**:1472 (Oct. 29) 1923; (b) Raynaud's Disease: A Critical Review of the Minimal Requisites for Diagnosis, *Am. J. M. Sc.* **183**:187 (Feb.) 1932; (c) Raynaud's Disease Affecting Men, *Ann. Int. Med.* **5**:1387 (May) 1932. (d) Jäger.⁶⁹

126. Lewis, T.: Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation: A Variety of Raynaud's Disease, *Heart* **15**:7, 1929.

127. Allen and Brown (footnote 125 a, b, c).

128. Müller, G.: Conditions Resembling Raynaud's Disease in Patients with Tuberculosis of Both Hili: Two Cases, *Wien. med. Wchnschr.* **83**:1205 (Oct.) 1933.

disorder should be looked on as a syndrome occurring in a number of definite clinical entities as well as the typical idiopathic type.

Although a number of Maurice Raynaud's cases were in men, its predilection for younger women has been characteristic. Allen and Brown^{125c} comment on the rarity of the disorder in men. They found 7 typical conclusive cases in men in a total of 150. There were 10 more in which the diagnosis was probable, making a total of 12 per cent. They state that functional vascular diseases affect men about as rarely as thrombo-angiitis obliterans affects women.

Bernheim and Garlock¹²⁹ believe that disturbances in calcium metabolism are factors in the development of Raynaud's disease and other vasospastic conditions. The reason for this is not entirely clear, but they think these phenomena develop in association with continued depletion of calcium and a negative calcium balance. Because of the unusual demand the parathyroid glands become hypertrophied, and continued hyperparathyroidism may result. In the earlier stages of the disorder adequate treatment with calcium in some cases resulted in considerable improvement. In others no benefit was obtainable. Six patients of this group, including some with Raynaud's disease and scleroderma, were subjected to parathyroidectomy. In 2 cases of uncomplicated Raynaud's disease astonishing improvement began immediately and has continued. In cases of scleroderma also considerable improvement has been noted. Assurance that a positive calcium balance continues post-operatively is necessary.

Lewis¹²⁶ has made many important observations. The reaction characteristic of Raynaud's disease occurs as a result of general or local exposure to cold. For the paroxysm to be produced by immersion of the hand in water, the temperature must be approximately 15 C. General exposure to room temperatures of from 13 to 18 C. was found to bring on the attack even when the patient was warmly clad and the hands were exposed.

Recovery in mild cases takes place quickly in a room temperature of 18.5 C. or more. The change in color from blue to red with a marked rise in temperature occurs rapidly as a result of relaxation of the affected vessels.

In more severe cases only partial recovery takes place at moderate room temperature, with partial temporary release of the spasm (intermittent leakage), resulting in arterial blood entering the cutaneous vessels and thus changing the color from blue to red. Little or no rise in surface temperature occurs. The color then returns to blue and fluctuates with the blood flow. At higher room temperatures the spasm is

129. Bernheim, A. R., and Garlock, J. H.: Parathyroidectomy for Raynaud's Disease and Scleroderma, *Ann. Surg.* **101**:1012 (April) 1935.

abolished. There is not necessarily a relation between color and temperature.

In severe cases there is persistent spasm at an ordinary room temperature, so that the temperature of the skin remains the same and the paroxysm is not relieved for long periods if the patient remains at rest. A high room temperature or increased physical activity is necessary to bring about relief. As a result of persistent spasms, blood flow is discontinued for a sufficiently long period to result in impairment of the integrity of the tissues, and dry gangrene of the tips may occur.

The normal reaction to overcooling, that is, by immersion in water at from 0 to 5 C., is reactive vasodilatation. In mild cases of Raynaud's disease the reaction is essentially normal. In the severer cases the reaction is modified by the tendency to vasoconstriction, especially at cooler room temperatures. The hand or fingers so treated become red but fail to show the typical rise in temperature of the normal extremity. The reaction is of the same type as that in the normal extremity, but is limited in extent and increased in duration, often being prolonged for several hours in a finger so exposed while in the other unexposed fingers spasm returns much earlier.

The site of the spasm in Raynaud's disease is in the digital arteries. No spasm exists in the veins; there is free passage of blood to the larger veins from the venules of the skin. The larger arteries of the hand are not usually affected.

Release of spasm occurs as the proximal parts to the spasm are warmed, resulting in the flow of warm blood to the vessels involved. Warming the distal portion does not release spasm.

In milder cases the arteries and arterioles of the fingers are intact, while in more severe cases complete dilatation does not occur but it is usually adequate.

Pallor and blanching of the skin appear in some attacks and indicate that the small vessels of the skin are empty. Cyanosis is more common. The circulation is shut off, but the small vessels in the skin contain blood from which oxygen is lost. In the presence of oxygenated blood the color is red. Blanching in some cases is infrequent and misinterpreted. Vasoconstrictor impulses to the minute vessels of the skin play no part.

According to these observations, paralysis of the vasoconstrictor nerves (by peripheral anesthesia) may not prevent spasm by exposure to cold, and spasm may be induced in susceptible vessels without nerve control.

When the vessels are in spasm and nerve block occurs with the release of normal vasoconstrictor tone, there is inhibition of normal vasoconstriction which allows warm blood to flow slowly into the fingers so that they become red without an increase in temperature. However,

at higher room temperatures this increase often is sufficient to tip the balance, and release occurs. Spasm is likewise more difficult to induce in nerve-blocked vessels because of the previous dilatation resulting from the release of normal tone and the consequent increased temperature.

The part played by the vasomotor nerves in the Raynaud syndrome when the spasm is induced by exposure to cold is definite, but it is not the primary cause. This consists of a local susceptibility in the vessels. The vasodilatation that follows nerve block is due to interruption of normal vasoconstrictor tone; some increased warmth results, and spasm is therefore less readily induced. In mild cases spasm under certain environmental conditions may be impossible, while even in severe cases the absence of normal vasoconstrictor tone may diminish the frequency of attacks.

This is further demonstrated, Lewis¹²⁶ says, by maintaining the hand in cold water with the temperature of the room fairly high. An abnormally high state of tone is induced in the vessels of the hand by immersion in cold water, but complete paroxysm does not occur until the room temperature is lowered. As a result of the additional increased vasoconstrictor tone which follows, complete spasm then results. The same degree of vasoconstrictor tone from low environmental temperature when the hand is at 30 C. is incapable of producing spasm. The vasomotor impulse excited reflexly by cold does not seem to be of unusual strength.

"It has been concluded from observation upon cooling of the fingers in cases of the type we have defined that an abnormality of the digital arteries exists; this displays itself in hypersensitivity of these vessels to relatively low temperatures."

The opposition to this conception of the pathogenesis of Raynaud's disease has arisen mainly from the observed effect of surgical interruption of the vasoconstrictor pathways with relief of the symptoms of the disorder in many cases by a number of workers.

Allen and Brown^{125b} as a result of their unusually large experience have expressed the opinion that the disease is ordinarily an equivalent of psychoneurosis or neurasthenia.

Simpson, Brown and Adson¹³⁰ in the early stage of uncomplicated Raynaud's disease found no evidence that the digital arteries or arterioles were at fault, and they believe that the abnormality is wholly in the vasomotor nerves. Interruption of the sympathetic pathway in these cases results in complete relief of symptoms. In more severe cases

130. Simpson, S. L.; Brown, G. E., and Adson, A. W.: Observations on the Etiological Mechanism in Raynaud's Disease, *Proc. Staff Meet., Mayo Clin.* **5**:295, 1931; Raynaud's Disease: Evidence That It Is a Type of Vasomotor Neurosis, *Arch. Neurol. & Psychiat.* **26**:687 (Oct.) 1931.

the authors believe that the digital arterioles are secondarily involved and show evidence of increased susceptibility to cold, but primarily the causative factor is to be found in the vasomotor system, and the vessels show changes secondarily as the result of continued spasm. Adson¹⁴ comments on the fact that climate seems to have very little effect. The disorder occurs in persons in very hot regions, and persons suffering from the affliction have not obtained relief by moving to warm climates. Adson cites the results of interruption of the sympathetic pathway by sympathectomy with complete relief from symptoms in many cases and almost universal relief in the lower extremities. This has been corroborated by many others. The more frequent failures in the upper extremities in his own cases and others he attributes to difficulties in operative technic and anatomic variations which have resulted in inability to sever all the sympathetic fibers.

This view is supported by the observations in 3 cases reported by Spurling, Jelsma and Rogers.¹³¹ Extensive operations were carried out in 3 severe cases with relief of all the symptoms in the lower extremities, but with failure to secure permanent relief in the left upper extremity. The authors conclude that in certain cases of Raynaud's disease of the hands the condition is not curable or controllable by present-day operative measures on the sympathetic nervous system. They believe that the vasomotor system is primarily at fault and offer explanations similar to those of Adson. The authors state that the arterial pathologic changes which they observed are the result of recurrent continued angiospasm with involvement of the larger digital arteries more marked than that of the arterioles. These histologic observations consisted of thickening of the intima and media with hypertrophy of the smooth muscle fibers and separation of the layers by open spaces. There was complete obliteration of the small arteries proximal to the area of gangrene. The media of the arterioles contained hypertrophic smooth muscle cells.

Villaret and his associates¹³² agree that the essential vascular disturbance in Raynaud's disease is arterial spasm. In proof of this they cite their experiments, which showed release of the paroxysm in Raynaud's disease following the injection of acetylcholine, which is an arterial dilator, and failure to obtain any improvement with histamine, which acts on the capillaries. The arterial spasm is the phase of white syncope of the paroxysmal crisis. With the reflex capillary dilatation

131. Spurling, R. G.; Jelsma, F., and Rogers, J. B.: Observations in Raynaud's Disease with Histopathological Studies, *Surg., Gynec. & Obst.* **54**:584, 1932.

132. Villaret, M.; Justin-Besançon, L.; Cachera, R., and Boucomont, R.: Etude critique sur la pathogénie des troubles circulatoires périphériques: Deuxième syndrome de Raynaud, *Arch. d. mal. du coeur* **28**:1 (Jan.) 1935.

which follows the cyanotic asphyxial phase appears; this in turn disappears when the arterial spasm is released and arterial blood again enters the dilated capillaries, and the warm, red stage follows. In the asphyxial stage of the disease the appearance of the hand is almost identical with that in cases of acrocyanosis, but the essential differentiating factor, a low or normal venous pressure, in persons with Raynaud's disease is in contrast to the increased venous pressure of persons with acrocyanosis.

Villaret and his co-workers, in a review of the pathologic observations, strenuously oppose the view of Lewis that the fault lies in the local susceptibility of the vessels. While they admit that vascular lesions may be encountered, they say that these are usually reported to be in the smaller vessels of the skin while the essential localization of the spasm is in the digital arteries. Vascular changes are to be expected as a result of spasmodic crises repeated daily many times over a long period. Especially significant to them is the appearance of spasm of the blood vessels as a result of injury or irritation to the vasomotor nerves. The authors are convinced that the paroxysms of Raynaud's syndrome are entirely mediated by the sympathetic nervous system.

While it appears that the two views are not reconcilable, this may not be true. There are certain facts which lead one to believe that the fault may lie in any part of the neurovascular mechanism and that it is not always the same in all cases. The Raynaud syndrome, occurring atypically, it is true, in cases of thrombo-angiitis obliterans must be due to a local increase in vascular susceptibility to cold. In the case reported by Gagel and Watts¹³³ the typical syndrome developed in a patient with carcinomatous metastasis to the spinal cord. The response of typical Raynaud paroxysms in moderately severe cases to stimuli of emotion and pain, even at a relatively high environmental temperature, is so well known that comment is not needed. However, it is equally possible that the end-result is an exaggerated vascular response to a normal stimulus as that it is an excessive stimulus to a normal vessel which results in exaggerated vascular reaction.

Graham⁹⁷ suggests that, whether the original causative factor is a local vascular fault or of neurogenic origin, spasm of the small arteries occurs and structural changes in these vessels are responsible for the nutritional changes in the tissues characteristic of the severer forms of the disorder. Repeated minimal trauma, not sufficient to cause impairment in normal vessels, may be responsible for thrombosis of the small arteries and capillaries. This may end in defects in the tissue and may account for the local vascular fault, secondary rather than primary.

133. Gagel, A., and Watts, J. W.: Zur Pathogenese der Raynaudschen Gangrän. *Ztschr. f. klin. Med.* **122**:110, 1932.

Morton and Scott¹³⁴ present an excellent conception. They comment on the induction of attacks by exposure to the proper degree of cold as well as by reflex painful and psychic stimuli when environmental conditions are suitable. In some cases they have noted that psychic stimuli are more potent than exposure in the induction of a paroxysm, at least in regard to frequency.

In the main, Morton and Scott confirm the conclusions of Lewis and Landis¹³⁵ as to the degree of temperature necessary to produce the paroxysm, the progress of the attack and the changes of color which follow release of the spasm, as well as other reactions to temperature. They state: "It seems certain from these studies that the essential abnormality in Raynaud's disease is a local hypersensitiveness of the peripheral smaller arteries to cold, as Lewis has emphasized." They believe that the vasoconstrictor influence should be emphasized because it does play an important rôle, as shown by the initiation or accentuation of paroxysms by psychic and nervous influences. While Raynaud's disease is not primarily due to an abnormality of sympathetic innervation, the majority of attacks are initiated or accentuated by vasoconstrictor influences under the ordinary living conditions of these patients. Regional anesthesia always causes improvement in the circulation to an ischemic extremity, though in the more severe cases the most distal part might remain uninfluenced by it.

In fact, Morton and Scott express the opinion that a dual mechanism must be responsible for these spasms in the peripheral vessels: first, essentially a hypersensitiveness to cold and, second, vasoconstrictor influences of normal type, which are important in bringing on and maintaining attacks. Therefore, their removal may be effective in the prevention of the paroxysms or in the reduction of their frequency.

Allen and Brown¹²⁷ state what they regard as the necessary criteria for diagnosis. These are: (1) intermittent attacks of discoloration of the acral parts, (2) symmetrical bilateral involvement, (3) absence of clinical evidence of occlusive lesions of the peripheral arteries, (4) gangrene or trophic changes limited in a large degree to the skin, (5) two years as the minimal period of duration, (6) absence of organic disease to which the vasomotor changes might be secondary and (7) predilection of the disease for females.

SECONDARY VASCULAR SPASMS

In addition to the typical Raynaud syndrome several writers have described secondary vascular spasms of a more or less localized type,

134. Morton, J. J., and Scott, W. J. M.: Some Angiospastic Syndromes in the Extremities, *Ann. Surg.* **94**:839 (Nov.) 1931.

135. Lewis and Landis.⁴⁸ Lewis.¹²⁶

which are often more persistent in their action than paroxysmal. There may be an exaggerated type of response to cold.

Morton and Scott¹³⁴ list the nervous diseases in which they have noted angiospasm of the peripheral vessels. Among these are anterior poliomyelitis, hemiplegia in the later stages, spina bifida and amyotrophic lateral sclerosis. Angiospasm may also be consecutive to trauma of many different types, fractures, sprains and contusions, as well as to causalgia when the main nerve trunks are implicated. Hypersensitivity to cold is outstanding in cases of angiospasm of this type; it may continue long after the acute effects of the trauma have subsided. This tendency to spasm may then pass into a latent stage, only to recur when exposure to the proper degree of cold occurs. De Takáts and Mackenzie²⁶ point out syringomyelia, multiple sclerosis and other diseases of the central nervous system, as well as lesions of the peripheral nerves, neuritis, perineuritis and cervical rib, as possible causes.

In cases of cervical rib the symptoms are usually motor and sensory and less frequently vascular. Telford and Stopford¹³⁶ have described the symptoms in 3 typical cases. The arm most used was involved, and the index finger was the first to show gangrene. The sequence of events was initial pallor, coldness, numbness and gangrene. There was a cessation of all pulse below the junction of the axillary and brachial arteries. The occlusion was limited to those vessels receiving their vasomotor nerves from the somatic nerves and did not occur in the subclavian and axillary vessels, which receive their nerve supply from the perivascular plexuses extending into the arm.

There is considerable variation in the anatomic distribution of the sympathetic fibers, and it is only when these emerge in the lowest branch of the plexus in contact with the cervical rib that symptoms of a vascular nature develop as a result of irritation of the fibers. The anatomic changes in the vessels are explained by long continued spasm of the muscular coat with resultant interference with their blood supply by compression of the vasa vasorum and the development of pathologic processes in the walls of the vessel which predisposes to thrombosis. The thrombosis begins in the smaller vessels of the fingers and extends upward into the larger vessels.

Symptomatic recovery takes place following surgical removal of the cervical rib.

In another case¹³⁷ the reaction to immersion in cold water was blanching pallor, while the other hand was normal. The radial and ulnar

136. Telford, E. D., and Stopford, J. S. B.: Vascular Complications of Cervical Rib, *Brit. J. Surg.* **18**:557, 1931.

137. Blair, D. M.; Davies, F., and McKissack, W.: The Etiology of the Vascular Symptoms of Cervical Rib, *Brit. J. Surg.* **22**:406 (Jan.) 1935.

arteries were not palpable, but there was marked pulsation in the axillary artery, so that aneurysm was suspected. After operation this disappeared and pulsations returned in the other arteries. At autopsy a few days later, marked endoneural thickening and proliferation were noted in the first dorsal nerve and the inferior part of the lower trunk of the plexus where it was related to the cervical rib. This lesion was thought to be responsible for the irritation of the sympathetic fibers producing the widespread vasoconstriction.

DISEASE OF PERSONS USING THE PNEUMATIC HAMMER

The reports of cases of vasospastic disorder in the hands of persons operating the pneumatic hammer used by limestone cutters have served to redirect attention to this peculiar abnormality, which occurs particularly among limestone workers.¹³⁸ The hammer used is driven by air pressure and has a vibration frequency of from 3,000 to 5,000 a minute. The symptoms are blanching and numbness of the fingers which guide the instrument, particularly the fourth and fifth.

After about a year of manipulation of the hammer the attacks of "dead finger" begin to appear, usually on exposure to cold, especially in the morning or after work with the hammer is discontinued, almost never while the hammer is in operation. Even after years during which pneumatic tools have not been used the attacks may come on in the affected fingers when exposed to cold. Relief from the attack is afforded by rubbing or other methods of warming and, it is said, by operating the tool.

No serious phenomena follow; gangrene or impairment of tissue integrity do not occur. Most stonecutters who have the disorder pay little attention to it and consider it part of their occupation.

ERYTHROMELALGIA

Brown¹³⁹ considers this the most typical example of a primary vasodilatation disturbance. He considers it a disease entity which is often confused with the phenomena which occur in cases of polycythaemia vera, thrombo-angiitis obliterans, gout, low grade forms of cellulitis, peripheral neuritis or the overactive stage of Raynaud's disease, poisoning by arsenic and thallium and even arteriosclerosis. This confusion is

138. Hardgrove, M. A. F., and Barker, N. W.: Pneumatic Hammer Disease: A Vasospastic Disturbance of the Hands of Stone Cutters, Proc. Staff Meet., Mayo Clin. 8:345 (June 7) 1933. de Takáts and Mackenzie.^{26a}

139. Brown, G. E.: Vasodilation Disturbances Affecting the Extremities: A Clinical Study, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 1, p. 241; Erythromelalgia and Other Related Disturbances in the Extremities Accompanied by Burning Pain, Am. J. M. Sc. 183:468, 1932.

due to a misconception as to what constitutes erythromelalgia, and the term has been loosely applied to the syndrome of any red painful extremity with paresthesia.

True erythromelalgia is characterized by the following features:

1. Bilateral burning pain in the extremities, often occurring intermittently in attacks.
2. A sharp increase in the local temperature of the affected part, with redness, flushing and congestion varying in degree.
3. Production and aggravation of the distress by heat and exercise.
4. Relief by rest, cold and elevation.

The patient has attacks of vasodilatation, with huge increases in the flow of blood in the extremities affecting both the superficial and the deep vessels. Redness may or may not be a prominent feature, depending on whether or not the superficial vessels of the skin participate in the vasodilatation. That the larger vessels are involved seems to be indicated by the marked increase in the oscillometer readings during the attack.

The etiology is not known, but Brown believes that it is the result of some disturbance in the vasomotor centers which accounts for the bilateral distribution of the disease. In 10 of 85 cases of burning pain of the hands or feet the symptoms were found to fill the requirements for the diagnosis of erythromelalgia. There were 3 cases in which the phenomena were typical except that they occurred unilaterally.

In these cases, with the induction of an attack with exercise, heat or posture, the surface temperature would increase to 35 or 36 C. Pain would begin at about 33 C.; flushing of the skin usually accompanied this rise and often pulsation in the larger veins, hyperhidrosis and paresthesia. In 1 case a refractory period without symptoms of from seven to ten days followed severe attacks.

Calorimetric determinations of loss of heat in an affected foot in this case showed a change from 33 small calories per minute for the entire foot when normal to 205 calories per minute during an attack. This, Brown estimates, indicates an increase of more than 600 per cent in the flow of blood during the period of vasodilatation. The oxygen content of the venous blood of this foot showed a value of 57 per cent when normal, and during an attack this rose to an oxygen saturation point of 83 per cent, approaching that of arterial blood.

In another group of patients with degenerative vascular disease involving the central nervous system there were paresthetic sensations of heat and burning pain, numbness and tingling, often unilateral. However, the patients in this group failed to fulfil the requirements for the diagnosis of erythromelalgia, not showing the correlation of temperature with symptoms and, if they did, showing the onset of symptoms at

from 31 to 32 C. The patients failed also to show relief with a decrease in surface temperature.

The phenomena of vasodilatation which occur in cases of polycythaemia vera are emphasized by Brown, who states that in half the cases there was this major complaint of burning pain in the hands or feet due to a true vasodilator disturbance with increased heat production, elevated temperatures of the parts and marked redness during the painful periods. The change was often unilateral. When the disease was controlled by treatment with phenylhydrazine the symptoms disappeared and attacks could not be induced. Bleeding also sometimes gave dramatic relief from the symptoms. There was a rough parallelism between the volume of blood and the output of heat in an affected part.

Polycythaemia vera should be considered in every case in which burning pain in the extremities is a major symptom.

In direct contrast to this point of view is that of Lewis,¹⁴⁰ expressed in the report of his studies on burning pain. He is of the opinion that "so-called erythromelalgia" is not a disease entity, that it is a symptom complex seen in many disorders and is not necessarily associated with vasodilator phenomena but may be. He proposes the term erythralgia to denote the burning redness which he found to be of identical type in cases of dermatitis factitia, erythrocyanosis, chilblain, thrombo-angiitis obliterans, senile arteritis and so-called erythromelalgia. He believes this to be identical with that of chronic inflammatory states of the skin and of the skin injured by ultraviolet rays, freezing, burning, scratching and the like.

He found the reaction producing the characteristic symptoms to be the same regardless of the method by which it was produced. Particularly likely to set off the pain-producing mechanism was any method by which the temperature of the hands or feet might be increased beyond a certain critical point, which was somewhat variable in cases of different type but in 1 case was of the same degree as that which Brown found in his typical cases.

When the temperature was raised by immersing the feet or the hands in warm water the symptoms developed at nearly the same level in all succeeding experiments. The same thing happened when the extremities became warm as a result of warming of the body or when the temperature of the feet and hands was increased by exercise, such as walking. Friction had the same effect. The pain usually occurred as a result of an increase in temperature but would sometimes appear without such an increase. The conclusion was reached that, though vasodilatation

140. Lewis, T.: Clinical Observations and Experiments Relating to Burning Pain in the Extremities and So-Called Erythromelalgia in Particular, *Clin. Sc.* 1:175 (Dec.) 1933.

may be present with pain, it is not a necessary part of the mechanism. It is also pointed out that a rosy color alone is not evidence of vasodilatation without an increase in temperature and that vasodilatation does not occur when the affected extremity is dependent. Further, many other parts of the skin may show this reaction; it may be unilateral as well as bilateral, and the skin of the trunk is often involved. Urticaria factitia is a frequent accompaniment. Obstruction to the venous circulation was also an effective means of inducing the pain reaction, which subsided in a few minutes after release.

The explanation offered is that the skin in all these cases is in a "susceptible state;" that is, the condition giving rise to these symptoms is located in the skin itself. This susceptible state is the result of some injury or inflammation, perhaps chronic or residual, by which the capillaries and small vessels are reduced to a toneless condition which results in the reddening of the skin when the part is dependent and is due to passive congestion and not to vasodilatation.

The stimuli capable of producing pain in persons whose skin is in the susceptible state are: (1) increase in the temperature of the skin to a certain level normally insufficient to produce pain either by increased blood flow or application of heat from without, (2) extreme cold, (3) local friction and (4) tension when it comes with walking, caused by warming of the foot both by increased blood supply and by friction. When pain occurs in a limb allowed to hang down it is due to hydrostatic vascular tension.

Burning pain has for its underlying basis the release from damaged tissues of a natural substance which acts on the pain nerve endings and lowers the threshold of these to tension and heat, causing them to discharge pain impulses even at a moderate increase of temperature or tension from dependence of the limb.

Severe burning pain of the fingers in cases of Raynaud's disease can be caused by quick warming of the fingers occasioned by a return of blood to them when they are cold. The same phenomena are present in normal fingers if the range of temperature is sufficiently increased.

It seems that Brown has answered one of Lewis' important questions, which he says has not been satisfactorily answered: "Is the vasodilatation which may accompany pain an abnormal one?" Lewis says that no evidence has been presented to show that it is abnormal for the circumstances in which it occurs. However, in the case described by Brown¹³⁹ there were both an extraordinary increase in the blood flow during the attack and an increase in the oxygen tension of the venous blood to 83 per cent. These findings would surely indicate an associated abnormal vasodilatation.

Brown¹³⁹ also recognizes such conditions as Lewis describes. These he considers as burning paresthesias and sharply differentiates them from

erythromelalgia by the absence of evidence of marked vasodilatation, as indicated by high surface temperatures. He considers a surface temperature during attacks of 33 or 34 C. or more to be a requirement for diagnosis in addition to the other criteria which have been mentioned.

ACROCYANOSIS

This is a poorly understood condition which probably represents a secondary symptom complex, although a primary permanent form has been described.¹⁴¹ There is some confusion as to the mechanism of the local vascular disturbance, and the diagnosis is often mistaken. The syndrome is frequently seen but sometimes overlooked because of the few subjective symptoms and because there are no serious consequences.

Lewis and Landis,¹⁴² with their report of observations on a case of acrocyanosis, briefly reviewed some of the earlier reports with descriptions of the disorder. Boettiger¹⁴³ describes the condition occurring in patients with acromegaly. Layani¹⁴⁴ describes the condition mainly in women. The hands are a persistent blue-red from a little above the wrists, and the color increases somewhat in intensity distally. The skin is cold, and the palms sweat rather profusely. The condition of the skin is otherwise normal. Puffy swelling of the fingers and hand is sometimes seen. Parrisius¹⁴⁵ saw the venous limbs of the capillaries to be distended, as well as the venules of the subpapillary plexus. He could not see a flow of blood in the capillaries.

Observations on their case led Lewis and Landis to believe that the essential vascular defect in this condition is the result of increased tone of the arterioles of the skin of the hands at ordinary environmental temperatures. Because of this, the inflow of the blood to the capillaries is diminished, oxygen is released and the superficial vessels, both capillaries and venules, are filled with blood which has lost oxygen. These investigators found the hands constantly cold and cyanotic, which they felt was due to stasis in the small vessels. Observations on the capillaries confirmed this.

Likewise, they were able to demonstrate that the defect was arterial and spasmodic, since the vessels were capable of normal dilatation if

141. Villaret, M.; Justin-Besançon, L. Cachera, R., and Boucomont, R.: *Etude critique sur la pathogénie des troubles circulatoires périphériques: Les acrocyanoses*, Arch. d. mal. du coeur **27**:725 (Dec.) 1934.

142. Lewis, T., and Landis, E. M.: *Observations upon the Vascular Mechanism in Acrocyanosis*, Heart **15**:229, 1930.

143. Boettiger: *München. med. Wchschr.* **46**:1733, 1899; quoted by Lewis and Landis.¹⁴²

144. Layani, F.: *Les acrocyanoses*, Paris, Masson & Cie, 1929.

145. Parrisius: *Deutsche Ztschr. f. Nervenhe.* **72**:310, 1921; quoted by Lewis and Landis.¹⁴²

the increased tone was released by increased environmental temperature. In contrast to the findings in persons with Raynaud's syndrome, histamine caused release of the spasm, resulting in an increased surface temperature which fixed the location of the obstruction in the arterioles.

Direct observations of the pressure in the venous capillary limbs gave results essentially the same as those noted in normal persons with a normal rise and fall after the obstruction and release of the venous return flow of blood. Lewis and Landis therefore concluded that the venous portion of the circulation is not responsible.

That vasomotor increase in tone is not responsible but that the cause is in the arterioles themselves is also concluded. Anesthetization of the ulnar nerve brings a late change only in color but a normal increase in temperature. The delay is interpreted as indicating that the deeper anastomotic vessels of the fingers open, allowing an increased flow of blood to warm the finger. The arterioles then respond to the warmth by a release of tone. The color reaction can be returned to the cyanotic tone when the vasomotor pathway is blocked, by immersion of the hand in water at 17 C.

The only explanation offered by Lewis and Landis as to the actual etiology is that the phenomenon is the result of impairment of the function of the superficial vessels of the skin as a result of exposure to cold, since only the exposed portions of the hands seem to be affected.

Villaret and his associates¹⁴¹ present a different conception of this condition. According to their view, capillary and venous dilatation constitutes the essential physiopathologic characteristic of acrocyanosis. They found a uniform increase in venous pressure in all cases. They believe the underlying causes of the vascular phenomena to be either on an organic basis, particularly with involvement of the vasomotor center and the vasomotor nerves, or on an endocrine basis. Among the causes of the former type they include syringomyelia, tabes and myelitis and particularly stress the association with sequelae of encephalitis. Alterations in the peripheral nerves with various types of neuritis are not uncommon in acrocyanosis. On the other hand, the disturbance in the sympathetic nervous system which results in this peculiar vascular condition may be entirely functional, and this is most often the case, according to the authors.

With this vascular disorder there is often noted an endocrine disturbance—ovarian, thyroid and adrenal. The condition may appear in both sexes about the time of puberty. The authors are inclined to believe that some pituitary functional disorder is the background for this rather indeterminate condition and conclude that basically there is a glandular-sympathetic coupling in the etiology of acrocyanosis, which they prefer to designate a humeroneurosis.

As proof of their contention that the fault lies in the capillary venous side of the circulation, the authors offer the observations on venous pressure, the values for which they have found to be always elevated in cases of acrocyanosis, in contrast to the observations in cases of Raynaud's disease, in which the values are depressed during the spasm, rising again afterward. The authors consider observations of venous pressure to be a most important measure in the study of vascular disorders and believe that venous pressure is the only available yardstick of the phenomena of the capillary venous circulation.

Landis and Gibbon⁴³ found that by immersion of the opposite extremities in warm water the temperature of the affected extremities failed to rise as it does in normal persons. Nerve block, however, brought about a rise in temperature to the normal level of vasodilatation, and the color eventually returned to normal. The parts involved always returned to normal color when warmed. When histamine was pricked into the skin the region of the flare became red in sharp contrast to the cyanotic color of the surrounding skin. These observations also speak for arteriolar spasm as the principal mechanism in the condition.

Brown¹³⁰ has frequently seen the disorder in asthenic adolescent boys and girls or following chronic diseases, such as arthritis. He says that this condition, like other similar functional disorders, represents an exaggeration of the normal response of vessels of the surface to cold or psychic stimulation in that the thresholds of stimulation in the centers of the cord and brain are modified by disease, growth or glandular disturbances.

THROMBOSIS INDUCED BY EFFORT

This condition has been reported with increasing frequency.¹⁴⁶ It seems probable that the relationship of effort to thrombosis may be frequently overlooked and the condition considered thrombophlebitis. Matas,^{146a} in an excellent review of the literature, has given a clear description which should aid greatly in its recognition.

It is his opinion that trauma in some form, trivial or violent, is the essential cause of the pathologic process in the vast majority of cases. Injury to the vein may be brought about by stretching or by contusion. In the case of thrombosis of the axillary vein, which is the vessel most often involved, compression between the clavicle and the first rib may be important. Gout, chronic plumbism, the rheumatic state and a variety of infections may be predisposing factors, but in some cases no such condition can be found. In the majority of cases the clinical course

146. (a) Matas, R.: On So-Called Primary Thrombosis of the Axillary Vein Caused by Strain, *Am. J. Surg.* **24**:642, 1934. (b) Ballon, H. C.: Primary Thrombosis of the Axillary Vein, *Canad. M. A. J.* **31**:414 (April) 1935.

and cultures of the thrombus and blood fail to show evidence of infection.

Venospasm has been described. That obstruction of the lumen of the vein is not the sole cause of the impairment to venous return is indicated by the extraordinarily rapid development of edema in some cases. It seems as though irritation of the perivenous plexuses in the wall must be the cause of extensive venospasm. Several cases have been reported in which operation failed to reveal thrombosis or any actual occlusion; the vein was found to be in a state of rigid spasm, thus causing obstruction to the circulation. Thrombectomy was carried out and the damaged section of the vein removed. Vasomotor equilibrium was restored, and the consequent edema quickly disappeared.

The clinical features are characteristic. Marked edematous swelling of the arm appears immediately or, less often, at a varying interval after strain or repeated or long-continued muscular effort. The edema spreads rapidly over the whole arm without associated fever. There is no local inflammation or constitutional reaction. The skin may be livid or cyanotic. Collateral venous channels may be visible on the shoulder and the wall of the upper part of the chest. A palpable tender cord may be found in the axilla corresponding to the axillary vein. Hematologic studies in those cases in which they were carried out did not reveal any characteristic deviation from the normal. The frequency of relapse when the same type of occupation or effort is persisted in is characteristic. Horton,¹⁴⁷ in his carefully studied case, noted diminished oxygen saturation of the venous blood in the affected arm but no deviation from the normal in regard to findings in the blood. He states that polycythaemia vera must always be considered.

In regard to treatment, Matas concludes that in all cases in which the usual methods of treatment for thrombophlebitis are not effective an exploratory operation is indicated to uncover the nature of the lesion; thrombectomy should be performed if a clot exists or excision of the venous section involved, whether a clot is found or not.

LATENT PHLEBITIS

While no attempt is being made to cover the subject of thrombophlebitis, so-called latent phlebitis is probably of sufficient importance to be mentioned briefly. Whether or not thrombosis may occur without inflammation, it is likely that intravascular clotting may take place in veins as a result of certain alterations of the blood.¹⁴⁸ Injuries, chemi-

147. Horton, B. T.: Primary Thrombosis of the Axillary Gland, *J. A. M. A.* **96**:2194 (June 27) 1931.

148. Shevkunenko, V. N.: Anatomic Types of Veins and Experimental Thrombophlebitis, *Sovet. khir.* **5**:50, 1933; abstr., *J. A. M. A.* **102**:1348 (April 21) 1934. Nordmann, M.: Kreislaufstörungen und pathologische Histologie, in Kisch, B.: *Ergebnisse der Kreislaufforschung*, Dresden, Theodor Steinkopff, 1933, vol. 4. Nygaard and Brown.⁸⁸

cal or traumatic, as well as inflammatory reactions, are the principal causes. That infection may remain latent and activation of ancient infections may occur under suitable conditions has been emphasized by de Takáts¹⁴⁹ in a discussion of resting infection in varicose veins.

He mentions a group of cases in which infection had subsided to a point where there were no clinical signs, only to suffer activation later. He believes the source to be primarily infected teeth and tonsils, pelvic infections, varicose ulcers and acute infection of the respiratory tract, and mentions low grade infection of the adjacent tissue as well. Trauma, injections into the veins or an operation may induce an acute episode.

Schmidt¹⁵⁰ and Meyer¹⁵¹ have recently drawn attention to the importance of this condition. It is bacterial in origin, according to Meyer, and may be acute or chronic. It usually develops in a vein at the site of some previous inflammation, which may or may not have been evident. The patient is usually unaware of the condition and his complaints usually suggest rheumatic involvement. The condition is said to be exceedingly common. Foci of infection as well as injuries, Meyer also considered the usual sources.

Easy fatigue and cramplike pains in the legs, which are more often present at night, are sometimes complained of. "Barometric sensations" with aching pain accompanying changes of the weather are emphasized. Slight edema may occur at night, and local eczema or itching is an important sign. Pain is the cardinal symptom, and the deep veins of the lower part of the leg are sensitive to pressure. Observation has shown that tenderness can usually be elicited at points where the deeper veins of the foot and leg can be pressed on.

The condition can easily be confused with thrombo-angiitis obliterans, but an intact arterial circulation serves to differentiate it. Myalgias may cause confusion. Chronic arthritis is seldom associated with phlebitis, but with a mild acute condition in the joints the contrary is true, according to Meyer, who insists that such latent infections frequently furnish a focus of infection in cases of acute arthritis which is usually overlooked. With activation of such an infection acute deep thrombophlebitis may develop, with the usual picture of edema, fever, local pain and the like.

149. de Takáts, Géza: "Resting Infection" in Varicose Veins: Its Diagnosis and Treatment, *Am. J. M. Sc.* **184**:57 (July) 1932.

150. Schmidt, C. L.: Zur Diagnose der latenten Phlebitis in den unteren Extremitäten, *München. med. Wchnschr.* **82**:290 (Feb. 2) 1932.

151. Meyer, O.: Das Krankheitsbild der latenten Phlebitis, *Deutsche med. Wchnschr.* **61**:595 (April 12) 1935.

TREATMENT

No attempt can be made to consider all the numerous therapeutic measures applied in cases of peripheral vascular diseases. Some have rather general application; others are limited to particular purposes. Sometimes therapy can be directed etiologically. This is particularly true in the secondary types of vascular disease, for example, in those developing in the course of polycythemia vera, hypothyroidism and specific infectious diseases like syphilis or even rheumatic fever. Diabetic vascular disease must be treated from the point of view of diabetes as well as that of the blood vessels.

That associated cardiac disease, especially in cases of disturbances in mechanism, such as auricular fibrillation and decompensation,¹⁵³ which occur frequently in association with arteriosclerosis obliterans, must receive adequate attention is axiomatic.

The treatment of both acute and chronic foci of infection has been emphasized by many, and the importance of general management of the patient has been universally recognized. Careful attention to detail often marks the difference between success and failure.

As an important principle in the treatment of this group of disorders Reid²² states that every possible effort should be made to save an affected arm or leg during a critical period, because a circulatory balance will often eventually be established, and in the milder types or early stages of the disease many persons can be spared the development of gangrene by the application of simple therapeutic measures. This expresses the general conservative view which most of the workers in this field have mentioned. As a result of the application of proper measures, major amputations are necessary much less frequently than they were even a few years ago.⁷⁵

Many of the general principles of treatment are applicable to all types of organic occlusive disease. The age of the patient, the general condition and the type of pathologic process may bring into consideration special types of management. The care of the feet when circulation is only mildly impaired is as important as when impairment of the integrity of the tissue exists, regardless of the cause. The necessity of keeping them warm and dry and free from even such minor infections as might result from small abrasions and the avoidance of minor contusions have been emphasized repeatedly. Not only is it important to keep the extremities themselves protected from cold by the use of proper shoes and clothing, but the whole body must be kept warm because of the important rôle of the extremities in the conser-

152. Footnote deleted.

153. Samuels, S. S., and Feinberg, S. C.: *The Heart in Thrombo-Angiitis Obliterans*, *Am. Heart J.* 6:255 (Dec.) 1930. Footnote 26.

vation of body heat by means of the vasoconstrictor mechanism.¹⁵⁴ This is an important measure in cases of Raynaud's syndrome as well as in those of obliterative disease.

Rest, by which is meant rest in bed with the extremities in a horizontal position, has been particularly widely emphasized as of the utmost importance in all types of obstructive vascular disease.¹⁵⁵ Not only is this important, but it is necessary to find the level of greatest circulatory efficiency, which is usually from 10 to 15 degrees below the horizontal. Postural exercises¹⁵⁶ and contrast baths^{31a} are aids in increasing the circulation, particularly in the absence of gangrene. The use of the heat-cradle and baking appliances have long been advised.^{31a}

It has been found that the degree of heat applied is of importance, particularly in cases in the advanced stage, when gangrene or ulceration is present. Pain is often intensified by too high a temperature. Starr¹⁵⁷ found that the optimum temperature for the relief of pain is from 33 to 35 C. Temperatures higher than this increase the metabolism of the tissue, and thus a greater supply of oxygen is needed. The increase in circulation which would normally follow the increase in temperature fails because of the vascular disease, and circulation becomes inadequate.

To overcome these difficulties Starr devised a constant temperature foot-cradle by means of which the environmental temperature could be controlled exactly. In addition, oxygen could be supplied locally and arrangements for desiccation introduced within the chamber. The usefulness of the oxygen was questionable, but no doubt existed as to the value of the controlled temperature, and desiccation was useful, particularly in the presence of gangrene. The experience of Severinghaus¹⁵⁸ with a constant temperature foot-cradle without oxygen or desiccation has been similar and leaves no doubt as to the value of proper control of temperature.

The relationship of tobacco to vascular disease has been discussed with thrombo-angiitis obliterans. The evidence is so conclusive that no doubt can be felt as to the rôle which tobacco plays in producing peripheral vasoconstriction, even though the question of its exact rela-

154. Coller and Maddock.¹⁶ Maddock and Coller.²¹

155. Samuels, S. S.: Gangrene Due to Thrombo-Angiitis Obliterans, *J. A. M. A.* **102**:436 (Feb. 10) 1934. Brown, Allen and Mahorner.²⁵ Samuels.³⁰

156. Allen, A. W.: Recent Advances in the Treatment of Circulatory Disturbances of the Extremities, *Ann. Surg.* **92**:931, 1930. Buerger.²³

157. Starr, I., Jr.: On the Use of Heat Desiccation and Oxygen in the Local Treatment of Advanced Peripheral Vascular Diseases, *Am. J. M. Sc.* **187**:489 (April) 1934.

158. Severinghaus, E. L.: A Constant Temperature Foot Cradle, *Am. J. M. Sc.* **187**:509 (April) 1934.

tion to etiology is not settled. The observations previously discussed have again been corroborated by Lampson,¹⁵⁹ using both the temperature tests and the plethysmographic methods of measurement. He concludes, as have most previous workers, that smoking and inhaling cigaret smoke cause sudden marked peripheral vasoconstriction and that smoking is contraindicated in persons having peripheral vascular disease. This applies not only to persons with thrombo-angiitis obliterans, with which tobacco is usually associated, but to persons with any other types of circulatory impairment.

Induction of artificial fever by the intravenous injection of typhoid vaccine was popularized by Brown and his associates.²⁵ It is a widely used and useful form of therapy, the principal application of which in peripheral vascular diseases is in thrombo-angiitis obliterans. That general peripheral vasodilatation occurs during, and follows for several hours after, the fever is unquestioned. Its principal drawbacks are the initial chill with the attendant period of vasoconstriction, during which thrombosis has rarely occurred, the discomfort to the patient and the danger attendant to its use in older persons with degenerative cardiovascular or renal disease.^{31a} Brown has recommended the use of a special type of vaccine with which the chill is diminished.

De Takáts is of the opinion that chill and high fever are unessential and suggests that minimal doses of typhoid vaccine be employed. With these subreactional doses vasodilatation can be produced without fever or discomfort and with complete safety. The dose employed is from 100,000 to 1,000,000 bacteria. The dose must be cautiously increased when vasodilatation fails to occur.

This suggests, as does the experience of Maddock and Collier,¹⁵⁴ that other methods of producing vasodilatation by heat might be equally effective. Reid²² has also suggested the careful administration of thyroid extract, by which the metabolic rate might be increased. Keeping the patient in an environment of relatively high temperature has been suggested, by the use of the heat cabinet of Lewis¹² or the insulated blanket of Maddock and Collier¹⁵⁴ or by the application of other methods of raising the body temperature. Heat has also been applied by means of diathermy locally with definite improvement.¹⁶⁰

Intravenous injections of saline solution have been applied mainly in the treatment of thrombo-angiitis obliterans. Samuels¹⁶¹ briefly traced

159. Lampson, R. S.: A Quantitative Study of the Vasoconstriction Induced by Smoking, *J. A. M. A.* **104**:1963 (June 1) 1935.

160. Perlow, S., and Blakely, Katherine: Local Diathermy in Peripheral Vascular Disturbances, *J. A. M. A.* **101**:1869 (Dec. 9) 1933.

161. Samuels, S. S.: Gangrene Due to Thrombo-Angiitis Obliterans: Further Experiences with Treatment, *J. A. M. A.* **102**:436 (Feb. 10) 1934.

the use of various types and strengths of solutions, until Silbert¹⁶² recommended the use of a 5 per cent solution of sodium chloride. Solutions of lower concentrations are sometimes employed (from 2 to 3 per cent), especially in older patients. Samuels¹⁶¹ finds that after the injection of the hypertonic solution there is a consistent increase in the pulse amplitude and pulse pressure shown by the oscillometer. This method is not specific for thrombo-angiitis obliterans, but it is to be considered as a "mechanical aid in the enhancement of collateral circulation in the extremities." Improvement is said to be prompt, especially in milder cases. In the more severe cases 300 cc. of the solution is given intravenously daily until the gangrene or ulceration is healed.

Extracts of tissue have been introduced into the treatment of peripheral vascular diseases rather recently. Barker, Brown and Roth¹⁶³ have been able to confirm the work of their predecessors, which they briefly review, that intermittent claudication can be relieved by treatment with several extracts of tissue. They employed an insulin-free pancreatic extract, an extract of skeletal muscle, muscle adenosin phosphoric acid and adenosin. These substances were all given intramuscularly, and, in addition, the extract of skeletal muscle was given orally.

There was an increase in the time necessary to produce claudication, that is, a greater amount of exercise could be performed before the development of pain, with all the preparations. The best results were obtained with the insulin-free pancreatic extract, after the administration of which 92 per cent of 55 patients with thrombo-angiitis obliterans and arteriosclerosis obliterans showed an increase in the time necessary to produce claudication with the standard walking test employed. Similar results were obtained with the other preparations, but all the extracts proved somewhat less effective in the cases of arteriosclerosis than in those of thrombo-angiitis obliterans.

The composition of the extracts is not known. They had little or no effect on pain while the patient was at rest or on the pain of gangrene. It was impossible to demonstrate that the relief of claudication was due to vasodilatation, since there was no significant rise in surface temperature and the relief of pain was more marked than that afforded by drugs or other methods of producing vasodilatation. In this Barker and his associates are not in agreement with previous investigators. It would seem that the effect obtained is that of an increased ability of the muscle to work with the available blood supply. Many patients

162. Silbert, S.: The Treatment of Thrombo-Angiitis Obliterans by Intravenous Injection of Hypertonic Salt Solution, *J. A. M. A.* **86**:1759 (June 5) 1926.

163. Barker, M. W.; Brown, G. E., and Roth, Grace M.: Effect of Tissue Extracts on Muscle Pains of Ischemic Origin (Intermittent Claudication), *Am. J. M. Sc.* **189**:36 (Jan.) 1935.

seemed to do well with one injection a week. The therapeutic value of the extracts of tissues seemed to be restricted to those cases in which intermittent claudication was the main symptom.

Drugs which are of value in the treatment of peripheral vascular disease are few and somewhat limited in usefulness except those affording relief of pain. There are several which are capable of producing vasodilator effects.

Alcohol has been employed by Cook and Brown ¹⁶⁴ in doses of 05. cc. per kilogram of body weight, by which it is possible to produce a high degree of vasodilatation which in controlled subjects approaches that obtained with fever and anesthesia. The duration is short and its effect on healing slight. The principal usefulness of this procedure is said to be in cases of arteriosclerosis with occlusion, when it is of great value in the relief of severe episodes of pain. Amputation can often be obviated or delayed, and the procedure is especially useful in those patients who present a poor surgical risk. It is more effective than morphine in the relief of pain while the patient is at rest. It may also at times reduce or eliminate the chill which follows the intravenous injection of foreign protein.

Theobromine or its compounds ¹⁶⁵ administered in sufficiently large doses in some cases appears to be of value in producing more prolonged vasodilatation. Theophylline ethylene diamine has a similar effect. The principal value of these drugs is likewise seen in cases of arteriosclerosis obliterans in which vigorous measures are contraindicated. The drugs are not effective in all cases, but in a certain proportion they have been used successfully in the relief of symptoms, and with prolonged treatment less severe trophic lesions have healed. Intermittent claudication has been relieved in some cases, both of the arteriosclerosis and of the thrombo-angiitis obliterans variety.

Several recent reports have appeared on the use of papaverine in sudden arterial occlusion. If the experience of Denk ¹⁶⁶ is confirmed by others, it is an important drug. Denk stated that the results of administration of papaverine equaled those following embolectomy, in pulmonary as well as in peripheral conditions. He has used it intravenously, repeated at short intervals (two to three hours) if necessary and continued at longer intervals for several days. If there is no relief of symptoms after the first or second injection none may be expected. In his experience, the drug was ineffective if used more than from two

164. Cook, E. N., and Brown, G. E.: The Vasodilating Effect of Ethyl Alcohol on the Peripheral Arteries, *Proc. Staff Meet., Mayo Clin.* **7**:449 (Aug. 3) 1932.

165. Scupham, G. W.: The Effect of Theobromine on Peripheral Vascular Diseases: Clinical Observation, *Arch. Int. Med.* **54**:685 (Nov.) 1934.

166. Denk, W.: Zur Behandlung der Arterien Embolie, *München. med. Wchnschr.* **81**:437 (March 23) 1934.

to four hours after the embolism occurred, and in advanced cases of arteriosclerosis the results were not as good as in cases in which there was relatively little degenerative disease.

Allen and McLean¹⁶⁷ report the use of papaverine in 1 case, in which "the return of circulation to the right leg as a result of treatment with papaverine was the most striking and dramatic" they had observed. They believe that the rapid improvement can be explained only by the relief of widespread arterial spasm initiated by sudden arterial occlusion. They state that its use is not contraindicated and in view of the prompt results obtained think it a valuable measure in addition to treatment by positive and negative pressure or embolectomy.

In addition to embolism de Takáts¹⁶⁴ has employed papaverine for the relief of vasospastic episodes of other types of obliterative disease.

Acetyl-beta-methylcholine has been found by Starr¹⁶⁸ to be a more effective drug than acetylcholine. It is a much more stable compound and produces more prolonged effects. It can be given, and is effective, both orally and subcutaneously. Its effects are similar to those following stimulation of the parasympathetic nerves, and it also causes peripheral vasodilatation. After subcutaneous injection it has a prompt and vigorous action. When administered orally its effects are milder. No serious toxic effects of the drug have been noted, and all effects can be immediately abolished by atropine.

Starr has found the drug effective in terminating paroxysmal tachycardia when given subcutaneously. The vascular spasm of Raynaud's disease was relieved or prevented by the action of the drug given by mouth when the spasm was excited by mild degrees of cold. It was ineffective when the exciting degree of cold was severe. It causes a rise in the cutaneous temperature of normal persons and in some persons with thrombo-angiitis obliterans, and gives some relief from pain in persons in the pregangrenous state of obstructive disease even though no evidence of vasodilatation is demonstrable. Page¹⁶⁹ states that the central mechanism plays an important part in the vasodilator effect. He states that dilatation of the blood vessels of the hands and feet is so slight that it is disappointing from the point of view of therapy. The rise in temperature, he thinks, is inconsequential.

167. Allen, E. V., and McLean, A. R.: The Treatment of Sudden Arterial Occlusion with Papaverine Hydrochloride: Report of a Case, Proc. Staff Meet., Mayo Clin. **10**:216 (April 3) 1935.

168. Starr, I., Jr.: Acetyl Beta Methyl Choline: III. Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease with a Discussion of Its Action in Other Conditions, Am. J. M. Sc. **186**:330 (Sept.) 1933.

169. Page, I. H.: Acetyl-Beta-Methylcholin (Mecholin): Observations Concerning Its Action on Blood Pressure, Skin Temperature and the Heart, as Exhibited by the Electrocardiogram of a Hypertensive Patient, Am. J. M. Sc. **189**: 55 (Jan.) 1935.

Goldsmith and Brown¹⁷⁰ are encouraged by indications of the usefulness of the drug as a vasodilatator, the safety in its use, the ease of administration and its prolonged effect.

Calcium has been suggested recently in the treatment of vasospastic disorders, particularly in those in which the Raynaud syndrome occurs, including scleroderma and some cases of thrombo-angiitis obliterans. Bernheim and London¹⁷¹ comment on 4 mild atypical cases of the Raynaud syndrome in which improvement occurred with the patient on a program of high intake of calcium with a diet high in vitamins.

This idea has been carried on by Bernheim and Garlock.¹²⁰ They are of the opinion that calcium deficiency is an important factor in the etiology of angiospastic states. In mild cases of Raynaud's disease feeding the patient calcium improved the condition, and both in cases of Raynaud's disease and in cases of scleroderma parathyroidectomy with continued feeding of calcium postoperatively resulted in marked improvement.

Conwell¹⁷² used parathyroid extract and calcium gluconate in 4 cases of thrombo-angiitis obliterans in which there was hypocalcemia. Marked improvement followed this procedure, even though other methods had not been successful.

Of the physical methods of treatment perhaps the most important advance has been the development of automatic apparatus by means of which prolonged treatment of obstructive vascular disease can be maintained by means of alternating positive and negative pressure applied to an extremity. This method, with some minor differences but much the same in principle, has been developed independently by Landis and Gibbon¹⁷³ and Reid and Hermann.¹⁷⁴ Since the original reports, several later ones have appeared from both sources.

The apparatus of Landis and Gibbon consists of an aluminum box into which the extremity is sealed by a rubber cuff. Alternating suc-

170. Goldsmith, Grace A.: The Vasodilating Effects of Acetyl β -Methylcholine, *Proc. Staff Meet., Mayo Clin.* **9**:337 (June 6) 1934.

171. Bernheim, Alice R., and London, Isabella M.: The Treatment of Spasmodic Vascular Disease of the Extremities of the Raynaud Type, *Am. Heart J.* **7**:588 (June) 1932.

172. Conwell, D. V.: The Treatment of Intermittent Claudication and Thrombo-Angiitis Obliterans with Parathyroid Extracts, *J. Kansas M. Soc.* **34**:457 (Dec.) 1933.

173. Landis, E. M., and Gibbon, J. H. Jr.: Effects of Alternate Suction and Pressure on Circulation in the Lower Extremities, *Proc. Soc. Exper. Biol. & Med.* **30**:593, 1933; Effects of Alternate Suction and Pressure on Blood Flow to the Lower Extremities, *J. Clin. Investigation* **12**:9715, 1933.

174. Reid, M. R., and Hermann, L. G.: Treatment of Obliterative Vascular Diseases by Means of Intermittent Negative Pressure Environment, *J. Med.* **14**:200, 1933. Hermann, L. G., and Reid, M. R.: Paevex (Passive Vascular Exercise) Treatment of Obliterative Arterial Diseases of the Extremities, *ibid.* **14**:524, 1933.

tion and pressure are applied by means of electrically driven pumps. The latest report of Landis and Hitzrot ¹⁷⁵ indicates that with the technic employed by them rapid changes in pressure are accomplished for short periods. Suction at a negative pressure of 120 mm. of mercury is maintained for a period of twenty-five seconds followed by positive pressure of 80 mm. of mercury for a period of five seconds.

The Hermann and Reid ¹⁷⁶ apparatus is likewise automatic. A glass boot is used for application about an extremity, so that it can be elevated or lowered. A rhythmic change in pressure can be applied from 80 mm. of mercury negative to 20 mm. of mercury positive at any selected rate of alternation. The changes in pressure occur more slowly than in the apparatus of Landis and Gibbon.

When treatment by this method is carried out frequently enough it causes the smaller arteries and arterioles to dilate and become sufficiently large to carry the collateral circulation about obliterated or badly diseased arteries.^{176b} In all patients who received intensive treatment for two weeks or more, according to Hermann and Reid, there was a rise in cutaneous temperature when observed under controlled conditions. Much of the pain disappeared in more than 86 per cent of the cases, all of which were of the severe obstructive type. In a few only slight symptomatic relief was noted, and 1 patient stated that he was not relieved after three months of treatment.

The authors emphasize the point that treatment by passive vascular exercise ^{176b} should supplement the methods which experience has shown to be of value. This applies particularly to the prevention of infection and avoidance of the slightest injury.

Landis and Gibbon ¹⁷³ have shown in normal subjects under carefully controlled conditions that the flow of blood as indicated by cutaneous temperature is greater in the limb exposed to variations of pressure and conclude that to obtain maximal effects on the flow of blood there should be relatively brief periods of suction, intermittent brief periods of pressure and diminished vasoconstrictor tone. The last is thought to be necessary in order to have the reservoir for the incoming blood as great as possible. This these workers accomplish by enclosing one arm in an electric heating pad kept warm enough to produce slight general sweating.¹⁷³

175. Landis E. M., and Hitzrot, L. H.: The Clinical Value of Alternate Suction and Pressure in the Treatment of Advanced Peripheral Vascular Disease, *Am. J. M. Sc.* **189**:305 (March) 1935.

176. (a) Reid, M. R., and Hermann, L. G.: Conservative Treatment of the Arteriosclerotic Peripheral Vascular Disease, *Ann. Surg.* **100**:750 (Oct.) 1934. (b) Hermann, L. G., and Reid, M. R.: Passive Vascular Exercises: Treatment of Peripheral Obliterative Arterial Diseases by Rhythmic Alternation of Environmental Pressure, *Arch. Surg.* **29**:697 (Nov.) 1934.

Even in cases of peripheral vascular disease which has advanced to the place where there is no increase in circulation with the abolition of vasoconstrictor tone, Landis¹⁷⁷ has found it possible to increase the blood flow by this method. Cyanosis and pain while the patient is at rest are diminished at least temporarily, and in some cases indolent superficial ulcers have healed. In a more recent publication Landis and Hitzrot¹⁷⁵ report on the results in 29 cases. In most of these cases the patients had been treated previously by the usual methods without success. After treatment by suction and pressure, the authors were able to record the results in 20 patients as good. They regard this as significant. The findings in this group confirm those previously reported. Pain of ischemia while the patient was at rest was usually relieved during the course of treatment and gradually became less severe in the intervals between. Lasting relief was not observed in the presence of deeply extending gangrene, large sloughs or osteomyelitis. Ulcers began to heal soon after the institution of treatment. Intermittent claudication was benefited.

Landis and Hitzrot state that this form of therapy must be applied with caution, and they advise small changes in pressure at first. The presence of acute infection or abscesses is an absolute contraindication. If carefully used the method is of distinct value and is of service by increasing the flow of blood temporarily during episodes of pain or ulceration so that time is gained for the development of collateral circulation.

Shipley and Yeager¹⁷⁸ obtained good results. They extended the treatment to include gangrene caused by frost-bite, arthritis, ununited fractures and other conditions.

De Takáts¹⁷⁹ used the method of Hermann and Reid. He agrees that a temporary increase in blood flow can be obtained in the presence of organic obstruction even in the case of a peripheral vascular bed which can hardly dilate. Improvement is obtainable in patients for whom no other therapy than amputation is helpful. He has given as his impression that the cases in which response is best are those in which there is involvement of the smaller vessels, in contrast to the experience of Hermann and Reid.^{176a} Although de Takáts' experience was not satisfactory with the group of cases of sudden organic occlusion, he is of the opinion that if used early this form of treatment may tide over periods of

177. Landis, E. M.: Observations on the Diagnosis and Treatment of Peripheral Vascular Disease, *Ann. Int. Med.* **8**:282 (Sept.) 1934.

178. Shipley, A. M., and Yeager, G. H.: Passive Vascular Exercise in the Treatment of Peripheral Circulatory Disease, *Surg., Gynec. & Obst.* **59**:480 (Sept.) 1934.

179. de Takáts, Géza: Obliterative Vascular Disease, *J. A. M. A.* **103**:1920 (Dec. 22) 1934.

crisis with a minimal loss of tissue. The effect is essentially that of release of spasm in the collateral circulation. He warns against the use of this method in case of infections and particularly in cases of venous thrombosis, as well as in those of the infectious type of diabetic gangrene. Especially in acute cases of venous thrombosis in which temporary arterial spasm sometimes occurs is this type of treatment to be avoided.

SURGICAL TREATMENT: A CRITICAL REVIEW

BY DR. DE TAKÁTS

An increasingly conservative attitude in the surgical treatment of peripheral vascular disease is unmistakable. This is due, first, to an earlier recognition of disorders of the peripheral circulation. Only in the last few years have patients been seen and treated before they arrived at the terminal stage of gangrene. Second, a more thorough understanding of the conditions which cause impaired circulation lead to the adoption of surgical procedures which are intended to improve or correct the perverted function of the blood vessels. Third, with a better insight into nature's methods of compensating for impairment of circulation, the surgeon may attempt to fit his procedure to the natural methods of repair instead of interfering with them.

The considerable amount of work which has accumulated in the last few years may be grouped under three headings, namely: (1) surgical efforts to improve impaired circulation, (2) surgical efforts to alleviate pain in cases of peripheral vascular disease and (3) surgical methods of removing nonviable parts at the optimal time and at the optimal level.

SURGICAL ATTEMPTS TO IMPROVE PERIPHERAL CIRCULATION

Ligation of a Vein.—The origin and development of the therapeutic procedure of occluding the concomitant vein of an obstructed artery dates from experiences gathered in the World War.¹⁸⁰ Experimentally, Brooks and his associates¹⁸¹ have demonstrated in repeated series of observations that the simultaneous ligation of the vein protects from gangrene an extremity the main artery of which has been tied. Previous

180. Sehart, E.: Ueber die künstliche Blutleere von Gliedmassen der unterer Körperhälfte sowie über die Ursache der Gangrän des Gliedes nach Unterbindung der Arterie allein, *Med. Klin.* **12**:1338, 1916. Makins, G.: Hunterian Oration, 1917, *Lancet* **1**:249, 1917. Propping, K.: Ueber die Ursachen der Gangrän nach Unterbindung grosser Arterien, München. med. Wchnschr. **65**:388, 1918.

181. Brooks, B.; Johnson, G. S., and Kertthey, J. A., Jr.: Simultaneous Vein Ligation: Experimental Study of Effect of Ligation of Concomitant Vein on Incidence of Gangrene Following Arterial Obstruction, *Surg., Gynec. & Obst.* **59**:496, 1934.

to the emphasis given to this procedure by Makins of the allied armies and Propping of the German army, a number of individual reports of ligation of both an artery and the corresponding vein were made, but this procedure was carried out of necessity and with considerable trepidation as to the increased incidence of gangrene.

There is considerable disagreement both in the experimental and in the clinical studies as to the mechanism and value of the procedure. The following changes have been reported to take place after ligation of the vein when the artery was simultaneously occluded: increased systolic blood pressure,¹⁸² increased venous pressure,¹⁸² diminished volume flow of blood,^{182a} increased surface and deep temperature,¹⁸³ increased collateral circulatory bed¹⁸⁴ and diminished incidence of gangrene.¹⁸⁵ Clinically, Oppel, Lilienthal, Willy Meyer, Ginsberg, Morton and Pearse, Brooks and Johnson and Van Gorder and Silbert report favorably on the use of this procedure for relief of chronic arterial obstructions in such diseases as arteriosclerosis and thrombo-angiitis obliterans. Silbert¹⁸⁶ reports 16 cases, evaluates the results carefully and says that in 9 cases a definite benefit has been obtained. He defers a final conclusion until greater experience has been obtained. On the other hand, the experiments of Theis¹⁸⁷ and Mulvihill, Harvey and Doroszka¹⁸⁸ and the clinical observation of McNealy¹⁸⁹ do not indicate any beneficial effects from simultaneous ligation of a vein. A critical review of the literature was published in 1931 by Mulvihill, Harvey and Doroszka,¹⁸⁸ who concluded that the literature on experimental ligation did not furnish any definitely proved, sound physiologic basis for this procedure and that the ligation of an artery in the lower extremity of man is not followed

182. (a) Brooks, B., and Martin, K. A.: Simultaneous Ligation of Vein and Artery: An Experimental Study, *J. A. M. A.* **80**:1678 (June 9) 1923. (b) Holman, E., and Edwards, M. E.: A New Principle in the Surgery of the Large Arteries, *ibid.* **88**:909 (March 19) 1927.

183. Morton, J. J., and Pearse, H. E.: Temperature Effect of Popliteal Vein Ligation in Thrombo-Angiitis Obliterans and Arteriosclerosis, *Ann. Surg.* **88**:233, 1928.

184. Pearse, H. E.: A New Explanation of the Improved Results Following Ligation of Both Artery and Vein, *Ann. Surg.* **81**:850, 1925.

185. Brooks, Johnson and Kerthey.¹⁸¹ Holman and Edwards.^{182b}

186. Silbert, S.: The Value of Femoral Vein Ligation in Chronic Arterial Obstruction, in *Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues*, New York, International Press, 1932, vol. 3, p. 1079.

187. Theis, F. V.: Ligation of Artery and Concomitant Vein in Operations on the Large Blood Vessels, *Arch. Surg.* **17**:244 (Aug.) 1928.

188. Mulvihill, D. A.; Harvey, S. C., and Doroszka, V.: Simultaneous Ligation of Vein in Ligation of Large Arteries, *Am. J. Surg.* **13**:431, 1931.

189. McNealy, R. W.: The Place of Elective Vein Ligation, *Surg., Gynec. & Obst.* **40**:45, 1925.

by a very high incidence of gangrene; in fact, it nearly approaches the 6.6 per cent. given by Halsted¹⁹⁰ as the incidence of gangrene in cases in which ligation of the common iliac artery was carried out.

The confusion and conflicts of opinion arise chiefly from the fact that different types of patients were subjected to ligation of the vein. In cases of arteriovenous aneurysm the ligation of both the artery and the vein, preferably proximally and distally, is a well established procedure.¹⁹¹ In acute cases of vascular occlusion resulting from a traumatic injury of the artery it is worth while considering that the temporary increase in venous pressure following ligation of the vein may be of aid in the critical period of developing collateral circulation. It may also release, at least in part, the spasm of the collateral vessel occurring in cases of acute vascular occlusion. In cases of chronic vascular occlusion, however, the possible benefits derived from this procedure are questionable. In addition, there is a possibility of a descending thrombosis reaching as far as the small veins, which certainly does not favor collateral circulation and which may even predispose to moist gangrene.

Generally speaking, ligation of a vein has not been of definite demonstrable benefit in cases of chronic vascular disease. Its main indication lies in the surgical procedures for aneurysms.

Periarterial Sympathectomy.—The stripping of the adventitia of the main nutrient artery of a part was chiefly popularized by Leriche.¹⁹² His initial publication stimulated a vast amount of work in continental Europe, and with undue enthusiasm a wide variety of clinical conditions have been included among the indications. According to reports by his school and a group of German investigators,¹⁹³ this operation has been successful in cases of causalgia, Raynaud's disease, trophic and traumatic ulcer, various kinds of cutaneous edema and cutaneous diseases, arthritis and delayed healing of bone. Later, a certain skepticism in regard to the permanent benefits became evident. Among others, Bernheim¹⁹⁴ reported on 30 cases of periarterial sympathectomy for circulatory disturbances of the extremities. In 11 the operation was regarded as a success and in 17 as a failure.

190. Halsted, W. S.: The Effect of Ligation of the Common Iliac Artery on the Circulation and Function of the Lower Extremity, *Bull. Johns Hopkins Hosp.* **22**:191, 1912.

191. Footnotes 180 and 189.

192. Leriche, R., and Heitz, J.: Des effets physiologiques de la sympathectomie périphérique, *Compt. rend. Soc. de biol.* **80**:66, 1917.

193. Brüning, F., and Forster, E.: Periarterielle Sympathektomie, *Zentralbl. f. Chir.* **49**:913, 1922.

194. Bernheim, B. M.: Periarterial Sympathectomy in Circulatory Disorders of the Extremities, *Surg., Gynec. & Obst.* **50**:456, 1930.

Reports of similar and contradictory character could be multiplied almost indefinitely. More recently, a small group of investigators¹⁹⁵ have brought forth both experimental and clinical evidence that this operation increases vascularity and accelerates the formation of callus and bony union. Colp, Kasabach and Mage believe that a further trial of the operation is justifiable in cases of recent fracture in those regions in which delay in union is characteristic and in those cases of fracture in which union appears to be delayed. Fontaine and Herrmann describe a disease entity which is characterized by the loss of motor function, characteristic patchy and later diffuse osteoporosis and a coexistence of vasomotor disturbances and great pain. It is not easy to differentiate these cases from those of Sudeck's reflex atrophy or from those of causalgia. In most cases, at least in the early stage, there are hyperemia and increased oscillations. Fontaine and Herrmann advise periarterial sympathectomy if the disease is limited to the distal parts of the extremity but cervical and lumbar ramisection for the extensive forms of the disease.

In spite of these favorable reports, most writers agree that hyperemia produced by periarterial sympathectomy is evanescent and that whatever effect can be obtained, such as more rapid formation of callus, healing of ulcers and taking of skin grafts, must be accomplished within from two to three weeks. It is difficult to see, in the light of careful anatomic studies,¹⁹⁶ how stripping of a short segment of an artery can effect the innervation of the arterial tree, as fibers of both sympathetic and spinal origin join the peripheral arteries in segments from branches of the peripheral nerves. Numerous attempts have been made to explain the results obtained by this operation. Leriche and Robeneau¹⁹⁷ suggest that the vasomotor effects of a single unilateral operation extend to all four extremities and that vasomotor reflexes are initiated from the denuded artery and are afferent. The subsidence of pain has also been explained by various ingenious theories.⁴ Epicritically one may say that neither theoretical considerations nor uncontrovertible clinical evidence supports the lasting value of periarterial sympathectomy. The only exception to this may be the occasional case in which a fibrosed artery or vein maintains reflectoric vasomotor phenomena. The strip-

195. Colp, R.; Kasabach, H., and Mage, S.: Periarterial Sympathectomy in Fractures: An Experimental Study, *Arch. Surg.* **27**:658 (Oct.) 1933. Fontaine, R., and Herrmann, L. G.: Post-Traumatic Painful Osteoporosis, *Ann. Surg.* **97**:26, 1933.

196. Kramer, J. G., and Todd, T. W.: The Distribution of Nerves to the Arteries of the Arm, *Anat. Rec.* **8**:243, 1914. Potts, L. W.: The Distribution of Nerves to the Arteries of the Leg, *Anat. Anz.* **47**:138, 1915.

197. Leriche, R., and Robeneau, F.: Indications et résultats de la sympathectomie périartérielle dans la chirurgie des membres, *Paris chir.* **19**:191, 1927.

ping of such an obliterated vessel does release spasm of the vessel.¹⁹⁸ This question will be discussed further under the section and resection of obliterated vascular segments.

Leriche and his associates¹⁹⁹ review their results with various types of sympathectomy for chronic ulcers of the leg. It is apparent that their original claims have not been substantiated. Fair results have been obtained in cases of posttraumatic ulceration, excellent results in cases of varicose ulceration and poor results in cases of postphlebitic ulceration. The sympathectomies were combined with skin grafting. In the phlebitic group two fatal cases of embolism occurred.

Arterial Ligation.—Lewis and Reichert²⁰⁰ propose ligation of the femoral artery just distal to the origin of the deep femoral artery in patients with Buerger's disease, with the idea of stimulating collateral circulation and speeding it up to keep ahead of the impending gangrene. They report 1 case. In a later article²⁰¹ 7 cases are reported. In 4 cases there was distinct improvement; in 2 cases in which gangrene was present at the time of the operation, amputation became necessary, and in 1 case hemiplegia and death followed the operation.

Lewis explained the relief from pain as a result of putting the inflamed artery at rest and partly as a result of increasing the collateral circulation. That a diminution of the intravascular tension relieves vascular pain is often experienced after ligation of the saphenous artery above a painful area of phlebitis. But the fact remains that the blood flow is actually cut down by ligation of the femoral artery and that the procedure, especially in cases of thrombo-angiitis obliterans, may lead to a sudden massive thrombosis distal to the ligature. That a certain transitory effect on the periarterial sympathetic system is operating in all arterial ligations was the early observation of Jaboulay.²⁰²

Arterial Excision (Arteriectomy).—In 1915 Leriche resected an obliterated arterial trunk in a patient suffering from causalgia. The pain disappeared, and no relapse had occurred for seventeen months. Since this time, a number of communications have appeared from Leriche and his pupils. These are summarized with their present indications, experi-

198. Leriche, R., and Fontaine, R.: *Experimental Researches on Vasomotricity*, Am. J. Surg. **85**:641, 1927.

199. Leriche, R.; Fontaine, R., and Maitre, R.: *Résultats éloignés du traitement des ulcères jambes par les opérations sympathiques combinées aux greffes cutanées d'après 52 observations*, J. de chir. **45**:689, 1935.

200. Lewis, D., and Reichert, F. L.: *Collateral Circulation in Thrombo-Angiitis Obliterans: An Indication for Ligation of the Femoral Artery Just Distal to Profunda*, J. A. M. A. **87**:302 (July 31) 1926.

201. Lewis, D.: *Spontaneous Gangrene of the Extremities*, Arch. Surg. **15**: 613 (Oct.) 1927.

202. Jaboulay, cited by Kuntz, A.: *The Autonomic Nervous System*, ed. 2, Philadelphia, Lea & Febiger, 1934, p. 539.

mental and clinical results, in a recent monograph.²⁰³ Experimentally, resection of the femoral or external iliac artery produced a smaller drop in the temperature of the dog's limb than if the same vessel had simply been ligated. When the common iliac artery was tied moist gangrene occurred in a large percentage of cases and occasionally death, whereas resection of the same artery resulted in dry gangrene of some digits that readily healed after self-amputation.

Leriche states that the type of arteritis which follows trauma, local compression, freezing and localized emboli is suitable for arteriectomy. This interrupts the reflectoric vasoconstriction which originates in the periarteritic fibrosis and which is responsible for the cyanosis, sensitivity to cold and trophic changes. The diagnosis of such localized inflammation of a single artery was made by arteriographic examination.

It is obvious that such an operation is not indicated in the majority of cases of peripheral vascular disease. However, on the basis of experimental evidence it must be admitted that in the occasional case of accurately localized thrombosis the excision of such an irritating focus may relieve vasomotor phenomena. Because of this reflex, vasoconstriction can be effectively interrupted by sympathetic ganglionectomy, and the scope of this method is further restricted.

Sympathetic Ramisection.—In 1924 practically simultaneously this operation was proposed in three different countries. In Germany von Gaza described it for "neuropathic abdominal dysfunctions." In Australia Royle advocated it for spastic paraplegia, whereas in France Leriche wished to modify painful vasomotor and trophic phenomena. Theoretically this operation would be the optimal one to deprive an extremity of its vasomotor innervation, because it interrupts the gray rami connecting the ganglionated trunk with the peripheral nerves and leaves the ganglions with their visceral innervation intact. It has gradually become clear, however, that (1) the operation can practically never be complete, as gray and white rami are not easy to distinguish and there are innumerable anatomic variations and a large number of the gray rami supplying the leg arise from the sacral ganglions in the pelvis so that complete ramisection is impossible; (2) the postganglionic fibers which are cut by such an operation readily regenerate, and (3) the much feared removal of the sympathetic ganglions and intervening trunk does not produce lasting or significant changes in the normal viscera deprived of their sympathetic nerve supply. On the contrary, when evidence of sympathetic overbalance is demonstrable the condition is benefited by ganglionectomy.

203. Leriche, R., and Stricker, P.: *L'artériectomie dans les artérites oblitérantes: Etude expérimentale et thérapeutique*, Paris, Masson & Cie, 1933.

For these reasons ramisection is thought to be improved by the addition of section of the sympathetic trunk, thus interrupting the pre-ganglionic outflow from the cord.²⁰⁴ Although this operation gives better results than ramisectomy alone, it is justly criticized on two grounds:²⁰⁵ First, the trunk, if merely cut across, is capable of regeneration, and the effects may be temporary, and, second, it has been shown ever since the time of Claude Bernard that peripheral vasodilatation is maximal only if the cells of the postganglionic fibers are removed.

The only satisfactory method, therefore, of removing the sympathetic supply to a limb is by ganglionectomy. As previously stated, the loss of visceral branches seems to have no ill effect on the patient. However, Danielopolu and his co-workers²⁰⁶ maintain that the removal of the stellate ganglion modifies the chromotropic and inotropic properties of the myocardium. Clinically, in many hundreds of cases in which bilateral cervicodorsal sympathectomy has been carried out, ill effects have not been observed.

Sympathetic Ganglionectomy.—This operation has gradually developed from an increasing conviction that lesser procedures, such as periarterial sympathectomy or ramisection, do not result in complete or lasting sympathetic denervation. Diez,²⁰⁷ Adson and Brown,²⁰⁸ Flothow and Swift,²⁰⁹ Stammers²¹⁰ and Telford and Stopford²¹¹ have observed large series. With increasing experience in sympathectomy, Diez in Buenos Aires and Adson of the Mayo Clinic postulate the treatment

204. Royle, N. D.: Sympathetic Trunk Section: A New Operation for Raynaud's Disease and Spastic Paralysis of the Upper Limb, *M. J. Australia* **2**:436, 1928.

205. Gask, G. E., and Ross, J. P.: *The Surgery of the Sympathetic Nervous System*, Baltimore, William Wood & Company, 1934, p. 64.

206. Danielopolu, D.; Marcou, I., and Proca, G. G.: Sur la physiologie du ganglion étoilé: modifications des propriétés fondamentales du myocarde provoquées par l'extirpation unilatérale ou bilatérale du première ganglion thoracique chez le chien, le coeur étant normal ou expérimentalement altéré, *Arch. de mal. du coeur* **22**:769, 1929.

207. Diez, J.: *La tromboangeitis obliterante*, Buenos Aires, El Ateneo, 1934.

208. Adson, A., and Brown, G. E.: The Treatment of Raynaud's Disease of the Upper Thoracic and Lumbar Sympathetic Ganglia and Trunks, *Surg., Gynec. & Obst.* **48**:577, 1929. Brown, G. E. Thrombo-Angiitis Obliterans: Buerger's Disease, *ibid.* **58**:297, 1934.

209. Flothow, P. G., and Swift, G. W.: Surgery of the Sympathetic Nervous System: Review of 100 Sympathetic Ganglionectomies, *Am. J. Surg.* **21**:345, 1933.

210. Stammers, F. A. R.: Some Experiences with Sympathetic Ganglionectomy, *Brit. J. Surg.* **20**:67, 1932.

211. Telford, E. D., and Stopford, J. S. B.: Remarks on the Results of Lumbar Sympathectomy in Thrombo-Angiitis Obliterans, *Brit. M. J.* **1**:173, 1933.

of peripheral vascular disease by sympathetic denervation which is as complete as possible. For the sympathetic denervation of the upper extremity, as Kuntz²¹² points out, it is necessary to cut the dorsal sympathetic trunk below the second dorsal ganglion because of a frequently communicating branch from the second ganglion to the first thoracic nerve. On the basis of these observations Adson evolved his technic of cervicodorsal sympathectomy from a posterior approach.²¹³ It also became evident from observations of Diez and those on my unreported cases that removal of the inferior cervical ganglion without the intermediate ganglion may lead to incomplete denervation or to Horner's syndrome, indicating that connections are possible between the cord and the intermediate ganglion. The anterior approach of Gask,²¹⁴ which permits exposure and removal of the intermediate and stellate ganglions with a section of the thoracic chain below the second ganglion, seems anatomically less injurious. Other technical modifications by Flothow and Swift,²⁰⁹ Leriche and Fontaine²¹⁵ and White, Smithwick, Allen and Mixter²¹⁶ illustrate that the surgical approach for cervicothoracic sympathectomy is still in the process of development, with an unmistakable effort at complete denervation. So far, Gask's method seems the most satisfactory.

For sympathetic denervation of the lower extremities the removal of the second, third and fourth lumbar ganglions is postulated through the anterior, transperitoneal,²¹⁷ anterolateral²¹⁸ and original posterior retroperitoneal approach.²¹⁹ For bilateral sympathectomy the transperitoneal

212. Kuntz, A.: Distribution of the Sympathetic Rami to the Brachial Plexus: Its Relation to Sympathectomy Affecting the Upper Extremity, *Arch. Surg.* **15**: 871 (Nov.) 1927.

213. Adson, A. W.: (a) Cervicothoracic Ganglionectomy, Trunk Resection and Ramisection by the Posterior Intrathoracic Approach, *Am. J. Surg.* **11**:227, 1931; (b) Changes in Technique of Cervicothoracic Ganglionectomy and Trunk Resection, *ibid.* **23**:287, 1934.

214. Gask, G. E.: The Surgery of the Sympathetic Nervous System, *Brit. J. Surg.* **21**:113, 1933.

215. Leriche, R., and Fontaine, R.: Technique de l'ablation du ganglion étoilé, *J. de chir.* **41**:353, 1933.

216. White, J. C.; Smithwick, R. H.; Allen, A. W., and Mixter, W. J.: A New Muscle-Splitting Incision for Resection of the Upper Thoracic Sympathetic Ganglia, *Surg., Gynec. & Obst.* **56**:651, 1933.

217. Adson, A. W., and Brown, G. E.: Treatment of Raynaud's Disease by Lumbar Ramisection and Ganglionectomy and Perivascular Sympathetic Neurectomy of the Common Iliacs, *J. A. M. A.* **84**:1908 (June 20) 1925.

218. (a) Rieder, W.: Resection der die unteren Extremitäten versorgenden Rami communicantes, *Chirurg* **5**:100, 1933. (b) Livingston, W. K.: The Clinical Aspects of Visceral Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1935. Flothow and Swift.²⁰⁹

219. Royle, N. D.: The Treatment of Spastic Paralysis by Sympathetic Ramisection: Experimental Basis and Clinical Results, *Surg., Gynec. & Obst.* **39**:701, 1924.

approach is most logical. In unilateral sympathectomy an anterolateral approach with the area under local anesthesia²⁰⁷ seems the safest and the one that allows exposure of the chain from the renal to the external iliac artery.

The results to be expected from sympathetic ganglionectomy in peripheral vascular disease may be gaged before the operation by the use of various tests for organic or spastic vascular occlusion. Whatever test is used, it only measures the reserve capacity of the peripheral vascular bed following immediate inhibition of the vasoconstrictor nerves. These tests do not indicate the end-results, as they do not allow time for the degeneration of postganglionic fibers or for the restoration of an intrinsic tonus of the wall of the vessel.

The physiologic effects of complete sympathetic denervation have been described as follows: There is an absence of sweating in the denervated area, which can be tested by Minor's method with starch and iodine²²⁰ or more conveniently by the use of cobaltous chloride.²²¹ For more exact determinations the measurement of resistance of the skin can be employed.²²² As the nerve fibers which control sweating and vasomotor impulses run a parallel course these tests for sweating constitute a simple clinical estimation of the completeness of sympathectomy.

The vasomotor phenomena following sympathectomy in extremities with normal blood vessels run a biphasic course. An immediate reaction, which lasts from three to twenty-one days, consists of flushing of the skin and increased pulsations,²⁰⁵ increased oscillometric curves,²⁰⁷ increased plethysmographic curves of the digits,¹⁵ distention and pulsation of an enlarged capillary bed,²²³ increased elimination of heat and a rise in surface temperature.²²⁴ In a second stage, which usually begins in the second or third week, the skin becomes pale, the visible capillaries are contracted but show a rapid flow and the plethysmographic tracings of the digits show a return to the preoperative rate of pulsation. The vessels regain their tonus, a fact first demonstrated in 1874.²²⁵

220. Minor, V.: Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung, *Deutsche Ztschr. f. Nervenhe.* **101**:302, 1928.

221. Roth, Grace M.: A Clinical Test for Sweating, *Proc. Staff Meet., Mayo Clin.* **10**:383, 1935.

222. Soloman, A. P., and Fentress, T. L.: Galvanic Skin Reflex and Blood Pressure Reactions in Psychoneuroses, *J. Nerv. & Ment. Dis.* **80**:163, 1934.

223. Brown, G. E.: Observations on the Surface Capillaries in Men Following Cervicothoracic Sympathetic Ganglionectomy, *J. Clin. Investigation* **9**:115, 1930.

224. Brown, G. E., and Adson, A. W.: Physiologic Effects of Thoracic and of Lumbar Sympathetic Ganglionectomy or Section of the Trunk, *Arch. Neurol. & Psychiat.* **22**:322 (Aug.) 1929.

225. Goltz, F., and Freusberg, F.: *Arch. f. exper. Path. & Pharmacol.* **9**:174, 1874.

When preganglionic fibers have been sectioned, degeneration of the postganglionic fibers does not take place, and the erector pilae muscles of the hair follicles can be made to contract and produce goose-flesh on direct stimulation with a faradic current,²²⁶ which, however, is not possible when postganglionic section has been performed. Thus, after cervicothoracic sympathectomy, direct pilomotor response cannot be elicited on the arm but is present on the face, because the postganglionic fibers arising in the intact superior cervical ganglion remain intact.

Another way to differentiate between preganglionic and postganglionic section is by the test for sensitivity to epinephrine, first demonstrated on the iris by Meltzer and Auer,²²⁷ but recently emphasized and elaborated in the case of peripheral vessels by James White and his co-workers.¹⁷ They have shown that an intravenous injection of 1 part of epinephrine in 250,000 parts of physiologic solution of sodium chloride injected at a rate of from 40 to 60 drops a minute will cause striking vasoconstriction in the extremities, with complete postganglionic denervation, but not when the operation is incomplete or if the section is preganglionic.

Clearcut evidence of increased blood flow in the sympathectomized extremity, which seems to persist indefinitely, has been furnished by Herrick, Essex and Baldes,²²⁸ who measured the minute volume in the femoral artery of the dog with Rein's *Thermstromuhr* and found it to be about twice as great in the sympathectomized extremity as in the control extremity. In addition, Gaskell,²²⁹ Hinsey²³⁰ and Theis²³¹ have brought forward indirect experimental evidence of persistently increased blood flow after a sympathectomy. Measurements of blood flow with the modification of the method of Hewlett and Van Zwaluwenburg have been made in a number of cases on the sympathectomized extremity by Diez.²⁰⁷ His measurements on man are the most clearcut evidence for permanently increased blood flow in the sympathectomized limb.

Results of sympathetic ganglionectomy for various vasomotor disturbances are gradually accumulating. There is agreement in the litera-

226. Lewis, T., and Marvin, H. M.: Observations upon a Pilomotor Reaction in Response to Faradism, *J. Physiol.* **64**:87, 1927.

227. Meltzer, S. J., and Auer, C. M.: Studies on the "Paradoxical" Pupil-Dilation Caused by Adrenalin, *Am. J. Physiol.* **11**:28, 1904.

228. Herrick, J. F.; Essex, H. E., and Baldes, E. J.: The Effect of Lumbar Sympathectomy on the Flow of Blood in the Femoral Artery of the Dog, *Am. J. Physiol.* **101**:213, 1932.

229. Gaskell, W. H.: *The Involuntary Nervous System*, New York, Longmans, Green & Co., 1916.

230. Hinsey, J. L.: Observations on Skin Temperatures in Hind Limbs Deprived of Their Sensory and Sympathetic Nerve Supply, *Am. J. Physiol.* **109**:53, 1934.

231. Theis, F. V.: The Effect of Sympathetic Neurectomy on the Collateral Arterial Circulation of the Extremities, *Surg., Gynec. & Obst.* **57**:737, 1933.

ture that (1) sympathectomies on the lower extremities are generally more successful than those on the upper extremities;²³² (2) that the early stage of Raynaud's disease, in which secondary obliteration of the digital or even larger vessels has not yet taken place,²³³ is the favorable stage for surgical intervention, and (3) that recurrences do occur, chiefly on the upper extremities, when evidence of organic involvement is available.

The causes of failure of sympathectomy in cases of Raynaud's disease have been carefully analyzed by James White in his recent monograph.²³⁴ Failure may be due to (1) incomplete denervation, which is more apt to occur in operations on the upper extremities, (2) a late stage in the course of the disease, in which obliterative arterial changes are present, and (3) sensitization of the completely denervated limb to epinephrine when postganglionic degeneration of the sympathetic fibers has taken place. Better results on the lower extremity are explained by the fact that after complete cervicothoracic ganglionectomy all postganglionic vasoconstrictor neurons degenerate and render the digital vessels highly sensitive, whereas, following the resection of the second, third and fourth lumbar ganglia, only the last neurons to the femoral and obturator nerves degenerate, while the postganglionic neurons to the sciatic nerve, which originate in ganglion cells of the fourth lumbar to the third sacral ganglion, are unaffected, and here a preganglionic section has taken place.

From these considerations one might draw the inference that pre-ganglionic section would be desirable for the upper extremity, but in order for this to be complete it would necessitate section of the anterior roots of the four upper dorsal segments.

Contrary to this opinion, Livingston tries to accomplish complete postganglionic section and degeneration. He suggests that an important cell station for the upper extremity may be found at the third thoracic ganglion, and removal of this structure would produce the most complete vasodilatation of the upper extremity. This operation clearly resembles then Royle's section of the trunk, which often leaves pre-ganglionic fibers from cord to stellate or from cord to intermediate ganglion unsectioned.

At present, available evidence both from the anatomic and from the physiologic standpoint tends to show that the removal of the intermediate, inferior cervical and first and second thoracic ganglia gives

232. Telford, E. D.: Sympathectomy: A Review of 100 Operations, *Lancet* 1:444, 1934. Adson,²¹³ Gask,²¹⁴ Livingston.^{218b}

233. Leriche, R., and Fontaine, R.: Sur le nature de la maladie de Raynaud, *Presse méd.* 40:1921, 1932. Spurling, Jelsma and Rogers.¹³¹

234. White, J. C.: The Autonomic Nervous System, New York, The Macmillan Company, 1935.

the most complete denervation for the upper extremities, and the excision of the second, third and fourth lumbar ganglions with the intervening trunk, the best denervation for the lower extremity. It is true that Oughterson, Harvey and Richter²³⁵ have shown that following a typical lumbar sympathectomy vasodilatation is not complete unless the sacral ganglions are blocked. Nevertheless, for practical purposes the excision of the sacral sympathetic chain is unnecessary.

With spasms of the secondary vessel of central or reflectoric origin, such as those which occur in cases of anterior poliomyelitis,²³⁶ of traumatic injuries to the spinal cord²³⁴ and of lesions of the pyramidal tract without muscular atrophy,²³⁴ the circulatory improvement is striking and permanent, although muscle spasticity is unrelieved. In experimental animals, when gangrene is threatened following arterial ligation or sudden thrombosis, inhibition of collateral spasm has saved the limb.²³⁷ In patients, however, the block of the prevertebral chain with procaine hydrochloride, to be discussed later, is simpler and is equally effective in its temporary effects.

Most controversy centers about the treatment of thrombo-angiitis obliterans by sympathetic ganglionectomy. Diez²⁰⁷ reports the cases of 150 patients and Adson the cases of over 100 patients with Buerger's disease on whom sympathectomy has been performed. In the former group there were 7 deaths: 2 of thrombosis of the abdominal aorta, 1 of a pulmonary abscess, 3 of bronchopneumonia and 1 of paralytic ileus. Diez attributes these to the use of general or spinal anesthesia and reports no deaths in the last series of 21 cases in which lumbar sympathectomy was carried out with the area under local anesthesia. In Adson's 6 fatal cases cardiovascular complications were prevalent. As to results, Diez reports recurrence or failure in 12 per cent of his total series, which dropped to 5 per cent in the last group of patients. Adson's results have been analyzed by Brown.^{213b} They are less favorable than those of Diez and also of those of Silbert,²⁴ who reports the largest percentage of cures obtained by his conservative treatment.

235. Oughterson, A. W.; Harvey, S. C., and Richter, H. G.: Observations on the Sympathetic Pathways, *Ann. Surg.* **96**:744, 1932.

236. Telford, E. D., and Stopford, J. S. B.: Some Experiences with Sympathectomy in Anterior Poliomyelitis, *Brit. M. J.* **2**:770, 1933.

237. Stricker, P., and Orban, F.: Recherches expérimentales sur la thrombose artérielle les artérites, la gangrène et sur le valeur comparée des ligatures artérielles et des artériectomies, *J. de chir.* **36**:697, 1930. Reickert, F. L.: Thermal Changes in Denervated and Sympathectomized Limbs With and Without Arterial Ligation, *Proc. Soc. Exper. Biol. & Med.* **29**:473, 1932. Oughterson, Harvey and Richter.²³⁵ Theis.²³¹

The attitude of Allen,²³⁸ Livingston,^{218b} and Gask and Ross²⁰⁵ has been more conservative. The difficulty of treating patients with Buerger's disease by sympathectomy is due not only to the fact that in the late stages very little spasm is evident and a diffuse arteriolar involvement is exhibited, but to the facts that the disease in the extremities is not arrested by sympathectomy and acute thrombotic occlusion with subsequent gangrene may occur in a previously sympathectomized lower extremity. While the absence of reflex vasoconstriction in the suddenly occluded limb is of definite benefit, the reserve capacity of the collateral bed is so small that the inhibition of the collateral spasm cannot make much difference. Finally, as some of these patients show vascular involvement in the viscera, heart, brain and spinal cord, the operation cannot be expected to effect a cure.

So long as relief from pain in the extremities, excluding amputation, can be obtained by other measures, such as will be discussed later, sympathectomy in patients with Buerger's disease is best limited to the upper extremities, when digital gangrene and intractable pain are present. Here peripheral injections of alcohol are not feasible, and the available collateral bed is so extensive that a certain stabilizing effect on the disease may be observed. The operation may offer quick demarcation of the parts, rapid healing and, often, relief from pain. The disease itself must be treated as a general systemic disturbance.

In ultimate analysis the results from sympathectomy in cases of Buerger's disease are not striking, and the mortality rate, which is negligible if the operation is performed for other conditions, is approximately 6 per cent. That sometimes striking results are obtained in chronic cases of endarteritis obliterans in the healed stage should be emphasized. In such cases spasm of the vessels is maintained from the plexuses of the periarterial nerves. Hence, the importance of distinguishing this type of vascular obliteration from that of Buerger's disease.¹⁰⁴

Embolectomy.—When the diagnosis of arterial thrombosis can be reasonably excluded and when the patient has been observed from six to ten hours after the sudden occlusion, embolectomy in a peripheral artery is justly considered. Pearse¹⁰¹ has given a complete review and analysis of the location of emboli and their incidence in 272 cases reported in the literature. The axillary and brachial arteries in the upper extremity, the aorta and the common iliac, femoral and popliteal arteries of the lower extremity are the most common sites of embolism. The prognosis depends on the cardiovascular status of the patient, on

238. Allen, A. W.: Results Obtained in the Treatment of Raynaud's Disease by Sympathetic Neurectomy and in Thrombo-Angiitis Obliterans by Desensitization of Peripheral Sensory Nerves, *Ann. Surg.* 96:867, 1932.

the extent of the collateral circulation at the obstructed level, on the early diagnosis and on operation during the early stage. Only a few hours are required before secondary arterial thrombi may occlude the peripheral branches of the artery. Also, the wall of the vessel reacts to emboli, so that a secondary thrombus may occur at the site of the removed embolus. Nevertheless, the collective review of the results of Pearse embolectomies performed within the first ten hours shows that the operation was successful on the upper extremities in 47 per cent of the cases, on the lower extremities in 40 per cent and in the pelvis in 31 per cent. Over half the patients subjected to embolectomy died within a month of the operation. This mortality was due either to the primary systemic disease, which was responsible for the embolism, or to emboli which later appeared in vital structures.

Two significant conservative measures, treatment by alternating negative pressure²³⁹ and the intravenous injections of papaverine,¹⁶⁶ or the two methods combined, are worthy of trial before embolectomy is decided on.

Adrenalectomy and Adrenal Denervation.—In their report at the forty-third session of the French surgical congress Leibovici and Stricker²⁴⁰ conclude that adrenalectomy in the treatment of obliterating arteritis lacks all physiologic basis, as hyperepinephrinemia is not demonstrable in Buerger's disease nor can the removal of one adrenal gland have any physiologic effect. It is impossible to demonstrate general or lasting vasodilatation following such an operation. This statement is timely and necessary as, following the insistence of Oppel²⁴¹ and Leriche,²⁴² unilateral adrenalectomy has been performed in over 100 patients in Europe. Their careful analysis by Leibovici and Stricker²⁴⁰ shows that the results are discouraging. It is interesting to note, however, that, according to White's recent work on the sensitization of sympathectomized vessels to epinephrine,¹⁷ the circulating hormone is capable of producing spasm of the vessels, which can be experimentally abolished by adrenal denervation.²³⁴

Results of adrenal denervation in cases of vascular disease are unknown. Crile²⁴³ states that the results do not as yet justify the application of this method in cases of Raynaud's disease.

239. Reid and Hermann.⁷⁴ Landis and Hitzrot.¹⁷⁵ de Takáts.¹⁷⁹

240. Leibovici, R.: La surrénalectomie dans le traitement de l'artérite oblitérante, *J. de chir.* **44**:525 (Oct.) 1934. Stricker, P.: Bases physiologic indications, et résultats de la chirurgie des surrénales, *ibid.* **44**:513 (Oct.) 1934.

241. Oppel, W. A.: Die Raynaud'sche Krankheit als Hyperadrenalämia, *Arch. f. klin. Chir.* **149**:75, 1928.

242. Leriche, R., and Stricker, P.: Place de la surrénalectomie dans le traitement conservateur des artérites juvéniles, *Presse méd.* **40**:1237 (Aug. 10) 1932.

243. Crile, G.: *Diseases Peculiar to Civilized Man*, New York, The Macmillan Company, 1934.

EFFORTS TO ALLEVIATE PAIN

While it is well established that sympathetic neurons carry only efferent motor impulses, it has been amply demonstrated that "visceral pain" can be relieved by block of the sympathetic nerves. This is due in part to the presence of large myelinated fibers of the somatic type within the sympathetic trunk.²³⁴ Evidence has also been brought forward²⁴⁴ that sympathetic motor impulses liberate tissue metabolites which in turn stimulate the sensory nerve endings of somatic nerves. Moore and Singleton²⁴⁵ have shown that pain originating from the arteries of the extremities traverses the somatic sensory nerves. In man, however, Foerster²⁴⁶ especially has insisted on afferent sensory pathways in the vessels. It has also been suggested that the stimulation of sympathetic fibers changes the threshold of sensibility of the somatic nerves.²⁴⁷

Peripheral Nerve Block.—The injection of alcohol²⁴⁸ and section and resuture²⁴⁹ or crushing²³⁴ of the peripheral nerves supplying the foot can be accomplished without motor paralysis, except that of the intrinsic muscles of the foot, which is unnoticed by the patient. The foot is completely desensitized, showing sensory and sympathetic paralysis, with the resulting vasodilatation and dryness. This vasodilatation is as great or almost as great as can be obtained by spinal anesthesia and may tide the patient over a critical and excruciatingly painful period. It does not relieve intermittent claudication. Its effect lasts from two to six months, at which time it can be repeated.

The incisions are made 6 inches above the ankle, and collateral circulation at this level must be adequate to insure primary healing. For complete desensitization of the foot, five nerves must be severed with meticulous technic. The drawback of the procedure is that an ascending infection, like a plantar abscess, may go unnoticed. Trophic ulceration, unless the nerves are completely severed, does not seem to occur.

244. Davis, L., and Pollock, L. J.: The Rôle of the Sympathetic Nervous System in the Production of Pain in the Head, *Arch. Neurol. & Psychiat.* **27**:282 (Feb.) 1932.

245. Moore, R. M., and Singleton, A. O., Jr.: Studies on the Pain-Sensibility of Arteries: Peripheral Paths of Afferent Neurones from the Arteries of the Extremities and of the Abdominal Viscera, *Am. J. Physiol.* **104**:267, 1933.

246. Foerster, O.: *Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände*, Berlin, Urban & Schwarzenberg, 1927.

247. Attenberger, H., and Kroll, F. W.: Ueber die vegetative Beeinflussung des somatischen Nervensystems, *Arch. f. d. ges. Physiol.* **223**:733, 1930.

248. Smithwick, R. H., and White, J. C.: Elimination of Pain in Obliterative Vascular Disease of the Lower Extremity: A Technique for Alcohol Injection of the Sensory Nerves of the Lower Leg, *Surg., Gynec. & Obst.* **51**:394, 1930.

249. Laskey, H. F., and Silbert, S.: Thrombo-Angiitis Obliterans: Relief of Pain by Peripheral Nerve Section, *Ann. Surg.* **98**:55, 1933.

This is a valuable procedure, especially adaptable to patients with Buerger's disease. In patients with diabetes or arteriosclerosis collateral circulation at the level of the incisions is often inadequate.

Paravertebral Block.—The use of this method to increase circulation and relieve pain in the extremities is relatively recent.²⁵⁰ The technic is readily mastered by those familiar with this form of conduction anesthesia. When small amounts of concentrated procaine hydrochloride fail to produce the desirable effect on circulation and pain, 5 cc. of 95 per cent alcohol is injected into the necessary segments. This method is especially useful in instances of intractable pain in the lower extremities of older patients with arteriosclerosis without gangrene, to gain a temporary increase in circulation after ligation or embolism of a large artery, and in cases of Buerger's disease in which peripheral nerve block is not feasible. In the upper extremity, because of occasionally unavoidable intercostal neuritis, pleurisy and pneumothorax, the use of this method is more restricted. The complete interruption of sympathetic pathways is difficult at operation, and much less can be expected from dorsal paravertebral injections. For injections of procaine hydrochloride to relieve pain in cases of causalgia or neuroma of the stump and to test the value of sympathectomy, the method is most valuable.

Intraspinal Injection of Alcohol.—This method²⁵¹ has been tested recently in several clinics and should be reserved for cases of intractable pain of the extremity when simpler methods have failed. Aside from malignant processes, intractable neuroma of the stump²³⁴ has been successfully treated. With careful technic complications have not been observed in a large number of cases.

Chordotomy.—Section of the spinothalamic tract for intractable pain in the extremities has seldom been carried out. The cases that have come to my knowledge or under my observation are not reported. Nevertheless, this possibility must be considered.

Amputations.—Technical improvements and mechanical considerations to improve the prosthetic value of the stump are outside the scope of this review. Extensive discussion of these problems can be found

250. Stern, E. L.: Alcohol Injection of Nerve Roots for Thrombo-Angiitis Obliterans, *Am. J. Surg.* **10**:107, 1930. Flothow, P. G.: Diagnostic and Therapeutic Injections of the Sympathetic Nerves, *ibid.* **14**:591, 1931. Reickert, F. L.: Intermittent Claudication Without Gangrene, Controlled by Sympathetic Nerve Block, *Ann. Surg.* **97**:503, 1933.

251. Dogliotti, A. M.: Traitement des syndromes douloureux de la périphérie par l'alcoolisation sub-arachnoïdienne des racines postérieures à leur émergence de la moelle épinière, *Presse méd.* **39**:1149, 1931.

in the new textbooks on surgery.²⁵² The indications, the proper time and the proper level of amputation in cases of peripheral vascular disease are of interest.

Amputation for intractable pain alone is hardly ever indicated since the advent of the special methods to relieve pain which have already been discussed. Amputation for restoring or improving function in a patient with a helpless, paralyzed part is an occasional consideration. But by far the most important indication for amputation is to remove a part which is hopelessly involved or which endangers the life of the patient because of absorption of toxins or spreading infection. With the advent of conservative methods which appeal to the patient and to the physician this last indication is often recognized too late and amputation is performed only as a hopeless gesture. Vascular disease still figures as the cause of about 30 per cent of all amputations in any large group of cases.²⁵² The incidence of amputations in cases of Buerger's disease is definitely decreasing with earlier diagnosis and adequate conservative treatment,²⁴ but even in Silbert's series the failure to avert a major amputation occurred in 9 per cent of his cases. Minor amputations, as the loss of digits, of course, are often necessary. If arterial thrombosis and embolism occur at unfavorable sites and if previously discussed conservative measures fail or are employed too late, amputation is required in a certain percentage of cases. The greatest percentage of amputations is performed in patients with arteriosclerotic or diabetic gangrene, those with the latter having an additional tendency to gangrenous infection and septicemia.

The determination of the peripheral vascular status and of the level of circulatory efficiency²⁵³ is most important. The most useful tests to determine the proper level of amputation are the estimation of the skin temperature and the study of the cutaneous reaction to histamine. These two tests almost invariably indicate an identical level.

Worthy of emphasis is the fact that there is no one single factor, observation or test by which the optimal level of amputation can be determined.²⁵⁴ The peripheral vascular status of the patient depends on age, the state of the cardiovascular apparatus and the immediate cause of the disease.

252. Kirk, N. T.: Amputations, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 3, chap. 10. Wilson, P. D.: Amputations, in Nelson Loose-Leaf Living Surgery, New York, T. Nelson & Sons, 1932, vol. 3, p. 563.

253. de Takáts, G.: The Determination of the Proper Level of Amputation, *Internat. J. Med. & Surg.* **47**:339 (Sept.) 1934.

254. McNealy, R. W., and Shapiro, P. F.: Vascular Disease of the Lower Extremities: Review of Amputations; Criteria, *Surg., Gynec. & Obst.* **59**:650, 1934.

In cases of diabetic gangrene, which tax the surgeon's experience and skill to the highest degree, an important distinction has been made between the condition that is primarily due to deficient circulation and that which is primarily due to infection.²⁵⁵ Naturally, both conditions may be present. While the former requires a major amputation, the latter is solved by minor amputation or sufficient drainage.

That education of the patient and close team-work between the physician and the surgeon are all-important is emphasized by Eliason.²⁵⁶ Spinal anesthesia was used in 80 per cent and local anesthesia in 17 per cent of 170 operations for diabetic gangrene. The operative mortality was 3.5 per cent, the hospital mortality was 41.8 per cent, and the mortality within one year was 55 per cent. This material from the records of a large charity hospital naturally gives the highest percentages of failure. Half the patients with diabetic gangrene were unaware of the presence of diabetes.

The last report of McKittrick and Root²⁵⁵ is more favorable. Again the importance of close team-work is obvious.

The growing tendency for conservatism in the treatment of peripheral vascular disease is obvious. But in the gangrenous state of older patients, especially in those with diabetes, conservatism must not lead to unnecessary delay in facing inevitable amputation. With accurate tests for collateral circulation the level and the optimal time of amputation may be determined on a safer basis than heretofore.

55 East Washington Street.

122 South Michigan Avenue.

255. McKittrick, L. F., and Pratt, T. C.: Principles of and Results After Amputation for Diabetic Gangrene, *Ann. Surg.* **100**:638, 1934.

256. Eliason, E. L.: Surgery of Diabetic Gangrene, *Ann. Surg.* **98**:1, 1933.

Book Reviews

Erbpathologie: Ein Lehrbuch für Aerzte. By O. Freiherr von Verschuer. Price, 8 marks; bound, 9 marks. Pp. 213, with 32 illustrations. Dresden: Theodore Steinkopff, 1934.

This book is the eighteenth volume of a series issued under the general title of "Medical Practice, a Collection of Special Subjects for the Improvement of Physicians." The idea is a good one, because each volume is written by a specialist well known in his particular line of work.

The pathology of heredity, or rather the pathologic conditions of the human body that can be transmitted by heredity, is perhaps no new problem even for those of the medical profession not versed in the complexities of mendelian transmission, but it is difficult for any one except the eugenicist to really understand them. However, every one who has had even limited clinical experience cannot fail to be impressed by the occurrence of undesirable physical and psychic departures from the normal, that are frequently impossible to handle satisfactorily, among patients who apply for diagnosis and treatment. The menace to racial health of hereditary ailments, or the predisposition to such ailments can be thoroughly appreciated only after long years of tedious statistical investigation and the coordination of numerous individual investigations and public sources of information.

Frankly admitting the defects in the present knowledge, Verschuer discusses his subject in a masterly way, not devoting more space to the theory of the transmission of genes than is absolutely necessary for a grasp on the subject matter of the succeeding text. This theoretical consideration includes a discussion of mendelian heredity and its application to man, including the mechanism of recessive and dominant characteristics, mutation, the development and transmission of hereditary disease anlage and the effect of peristatic (environmental) influences on the individual.

The section on special pathology considers briefly about two hundred and fifty diseases, disease groups or predispositions which experience and observation have shown to be more or less dominant or recessive in transmission.

The final sections of the book are devoted to suggestions relative to the special training of physicians and students in the diagnosis of hereditary disease and the establishment of clinics for the rendering of expert opinion in difficult cases. Existing legal provisions make it obligatory that physicians work in conjunction with certain prescribed courts the duty of which is to decree sterilization, forbid marriage, allocate funds, etc., to those whom the state for one reason or another regards as liabilities to the public weal.

The statute relative to the prevention of hereditarily diseased progeny was promulgated on July 14, 1933. Too short a time has elapsed to enable one to draw any definite conclusions. Whether it will have a salutary effect on public health remains to be seen. Sterilization is the keynote and is seemingly being applied without fear or favor. It appears rational, when one is reminded that there are estimated to be 450,000 feeble-minded, 280,000 persons with a schizophrenia and 20,000 or more afflicted with circular insanity within the Reich. All these ills fall within the category of dominant hereditary characteristics.

The burden of caring for this human wreckage is great for any country, and intelligent persons everywhere must ask themselves why these individuals should be allowed to propagate their kind unrestricted and to contribute their steadily increasing quota to the grand total of public enemies, delinquents and dependents. Doubtless Germany's experiment in Augean stable-cleaning will be watched with keen interest by all governments or organizations within the governments the interests of which center in the welfare of their people.

Verschuer's book, though somewhat difficult to understand by those not versed in the subject of heredity, contains much that can be read with considerable profit by all who think not so much in terms of the individual as of the stock.

Memoirs of a Small-Town Surgeon. By John B. Wheeler, M.D., Emeritus Professor of Surgery, University of Vermont College of Medicine. Price, \$3. Pp. 336, with 4 illustrations. New York: Frederick A. Stokes Company, 1935.

To enjoy the full flavor of these memoirs one must be a physician with a drop of New England blood in his veins and preferably one who appreciates the Harvard Medical School and the Massachusetts General Hospital. For this is a book of reminiscences with a background vividly colored by Vermont, Harvard and the "M. G. H."

The tale begins with the autumn of 1875, when Wheeler entered the Harvard Medical School. Brave days they were: Oliver Wendell Holmes was teaching anatomy; young Henry P. Bowditch, physiology; Calvin Ellis, medicine, and Henry J. Bigelow, surgery. Fine days they were, too, for the lucky "House-pups" at the hospital, who on graduation from the School were taken in hand and "licked into shape" by such strong personalities as C. B. Porter, Bigelow himself or John Homans. All M. G. H. men the entire country over are the same: To them there is only one hospital, and this is The Hospital; tales of old days can never be retold too often—tales of Bigelow and his lithotrite, of Jack Elliot with his brilliant mind and winning personality, of the accident room and the flat.

The second part of the book deals with postgraduate education abroad when it was the traditional thing for American fledglings to make the grand tour in Europe for a year or so before settling down in practice. One is elected to honorary membership in that intimate little Viennese club of Bostonians who dined regularly during the early eighties on beer and conversation at the Riedhof and occasionally took to its bosom an outsider like Halsted of Baltimore; who worked hard all day under teachers like Billroth or Zuckerhandl; who enjoyed the opera or Strauss waltzes at night. Gay, happy, care-free days they were!

The third part of the book tells how a self-respecting, intelligent man of good training can succeed in the practice of medicine, always provided that he has imagination, a certain amount of humor in his make-up and the will to win. Wheeler settled down in Burlington, gradually built up his practice and did in his lifetime all the things a good physician would like to do: had medical adventures in country farmhouses and bitterly drawn-out battles against death, became professor of surgery in the University of Vermont, did his share of public health work, conquered an epidemic of diphtheria, kept abreast of the times and changed his way of doing things as new ideas and technics became established.

The volume as a whole is a fine tribute to the medical profession. All medical students will enjoy it. It is a good tonic, too, for tired physicians who in the long winter evenings occasionally wonder what is the use of trying to practice medicine well. Throughout this account of a particularly varied medical experience spanning many years one feels constantly the joy of conscientious, tireless endeavor for fine ideals.

Physiology in Modern Medicine. By J. J. R. Macleod. Seventh edition. Price, \$8.50. Pp. 1154, with 297 illustrations. St. Louis: C. V. Mosby Company, 1935.

The seventh edition of this standard work in physiology appears after a lapse of five years. As this is a rather long interval from the time of the previous publication, there has necessarily been considerable revision of the text. One of the changes has been the removal of the word biochemistry from the title. Other new departures include the complete rewriting of certain chapters, a bibliography at the end of the volume instead of references at the end of each section and the addition of several new contributors.

Most of the sections have been written by Macleod. The rather long Part III has been extensively revised by E. P. Carter. The section on the endocrine organs has been revised by N. B. Taylor, and the section on the neuromuscular system, also quite long, has been rewritten by Philip Bard, whose name has not previously appeared in the list of co-authors. J. M. Peterson has revised the chapters on

the physicochemical basis of physiologic processes, and R. G. Pierce has assisted in the revision of Part II, devoted to the blood and lymph. J. M. Olmsted has written the section which has to do with special senses. It can be seen from this list of contributors and their contributions that the book is the composite presentation of several authors whose reputations in their special fields are as well established as is that of Macleod in his.

The book has been prepared with the express purpose of helping the clinician in applying physiology and biochemistry to medicine. This object has been kept in mind continuously by all the contributors, so that the book is not only an aid to the physiologist primarily and the student of physiology but also to the physician in the general field of medicine. The value of the book has been so well established that further comment hardly seems necessary. Unfortunately, the high standards of the contents of the book are negated in part by the extremely poor format. It seems a pity to spoil such a splendid scientific contribution by poor printing. Where changes have been made and new type has been used the result is a distinct difference in the degree of blackness, which makes for extremely difficult reading and spoils the appearance. The paper may be a poor type, because some of the illustrations taken from photographs are so indistinct and poorly reproduced that they would better have been omitted than incorporated.

Just at the time that this review was being prepared the death of Dr. Macleod was announced. It seems sad to think that this keen physiologist and brilliant scientist should have passed away at a comparatively young age. It is hoped that his book, however, will not die but will be continued by his co-authors and others who are interested in physiology, and that future editions will appear from time to time.

The Nervous Patient. By Charles P. Emerson, Research Professor of Medicine, Indiana University. Price, \$4. Pp. 453. Philadelphia: J. B. Lippincott Company, 1935.

New efforts in medicine always are interesting. Emerson has attempted something new in that as an internist he has put together a book which deals largely with the functional manifestations of disease and in so doing has invaded a field usually claimed by the neurologist or psychiatrist and rarely trespassed on by others. He has written his book with a definite purpose in mind: General practitioners are the ones in the profession of medicine who see organic and mental diseases in early stages when perhaps prevention or cure is possible, and he has dedicated the work to them, hoping evidently to arouse their interest in an important aspect of preventive medicine.

The book has a great deal of character and individuality. In parts it is much like a short textbook of general medicine with chapters on heart disease, pulmonary disease, genito-urinary disease and gastro-intestinal disease. These chapters are written, however, with especial emphasis on the various functional abnormalities which are likely to complicate the clinical picture of any chronic organic disturbance.

About half the book deals with "nervousness": disorders of sleep and of personality, the psychoneuroses and hysteria and, finally, the more serious "nervous" disorders, such as the manic-depressive psychoses and dementia praecox. The writing is simple and easy to follow; the printing is good, and the general appearance of the book agreeable to the eye and hand. On the whole, it can be recommended. Practitioners and students can learn a great deal from it.

Diabetes Mellitus and Obesity. By Garfield G. Duncan. Price, \$2.75. Pp. 227, with 40 tables. Philadelphia: Lea & Febiger, 1935.

Although insulin has been available for nearly fifteen years, most diabetic patients are still handled by the old Naunyn method of restricting carbohydrate. If insulin is prescribed, it is usually in a haphazard and inaccurate way, and the patient rarely eats a carefully weighed and measured diet. The cause of this unsatisfactory state of affairs is, the reviewer believes, evident: It is simple to

grasp the theoretical requirements of diet (and of insulin), but when it comes to translating a food formula into actual meals the ordinary physician fails miserably; he is, in fact, unable to do it. Hence unless he sees enough patients with diabetes to justify a special setup, including a dietitian-teacher for his patients, he follows the line of least resistance, which is to tell them not to eat sugar and starch and to give insulin in a vague and half-hearted way. Furthermore, the racketeers in the field of diabetes have written so much—each exploiting his own system of management—that most physicians are terrified into inferiority and withdraw behind the protection of inertia.

To remedy all this a great many small books have been written on diabetes, designed to make the treatment so simple for both patient and physician that any one can carry it out. The reviewer questions whether so far they have solved the problem.

In the present instance the reviewer has only praise to bestow. Duncan's book is clear, precise and sound and is stripped of complicated extraneous matter. It is a most useful work for the general practitioner to have on his table for quick reference in emergencies and to refresh his mind on diabetic problems.

Methods of Treatment. By Logan Clendening, M.D., Clinical Professor of Medicine in the Medical Department of the University of Kansas. Fifth Edition. Price, \$10. Pp. 879, with 102 illustrations. St. Louis: C. V. Mosby Company, 1934.

This is an interesting book with a colorful personality. When it made its début in 1924 its aim was to furnish physicians an outline of all the methods of treatment in internal medicine. Less was known then than now, so that the book was shorter and rather less profusely illustrated than at present, but otherwise it was of about the same general character. It created at once an enviable reputation. Each subsequent edition has been warmly welcomed, so that doubtlessly what was said of the fourth edition was no exaggeration (*ARCH. INT. MED.* 47:988 [June] 1931): "This book still remains the classic in the field of medical treatment for the practitioner and student. The lucid manner in which it is written and the fact that it includes every important field in medical therapeutics make it a necessary addition to any medical library."

The fifth edition keeps the volume fully up to the standard of its elders. Clendening states that the revision is the most thorough that has been made since the book was first set up. It appears to be very complete. Certainly this book continues to be delightfully written and has the proper appurtenances that a successful book should have in the way of good paper, clear printing and easily understandable diagrams. It will continue to be a highly respected and useful member of all self-respecting medical libraries.

Diseases of Children, with Contributions by 36 Authors. Edited by Hugh Thursfield and Donald Paterson. Third edition. Price, \$10. Pp. 1152, with 277 illustrations. Baltimore: William Wood & Company, 1934.

This is an English book distributed in this country. Nicely printed and profusely illustrated, it is a cooperative effort in the field of pediatrics similar to those of Cecil, Musser and Conybeare in general medicine. The result is an excellent miniature encyclopedia of pediatrics, but, as in all of these group compilations, one misses the personality and point of view of a single outstanding master. A vast field is covered, and there is of course considerable duplication of what is adequately discussed in textbooks of internal medicine. Hence, some of the articles on important topics are too brief to be of great value, and at times too much space is given to rare and curious conditions. On the whole, the book seems adequate, but it does not rouse one's enthusiasm.

ETIOLOGY AND TREATMENT OF SPRUE

OBSERVATIONS ON PATIENTS IN PUERTO RICO AND SUBSEQUENT
EXPERIMENTS ON ANIMALS

W. B. CASTLE, M.D.

BOSTON

C. P. RHOADS, M.D.

NEW YORK

H. A. LAWSON, M.D.

PROVIDENCE, R. I.

AND

G. C. PAYNE, M.D.

SAN JUAN, PUERTO RICO

In 1759 William Hillary¹ described a peculiar chronic type of diarrhea associated with sore tongue, pallor and emaciation which he had observed in Barbados. Then for nearly a century there appear to have been no further distinctive clinical accounts of the disorder. In 1864 Julien² enunciated the view that "Cochin-China dysentery" was a specific condition different from other forms of dysentery. Despite his arguments and the views of other first-hand observers,³ the French pathologists at home remained unconvinced. In 1880 both Manson,⁴ in Amoy, and

The observations on patients were carried out in 1931 by members of the Commission of the Rockefeller Foundation for the Study of Anemia in Puerto Rico; those on animals were performed subsequently at the Hospital of the Rockefeller Institute for Medical Research, New York.

From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard), Boston City Hospital; the Department of Medicine and the Department of Tropical Medicine, Harvard Medical School; the Hospital of the Rockefeller Institute for Medical Research, and the Presbyterian Hospital, San Juan.

1. Hillary, William: *Observations on the Changes of the Air and the Concomitant Epidemical Diseases in the Island of Barbadoes*, London, C. Hitch & L. Hawes, 1759.

2. Julien, C. -M.: *Aperçu sur les lésions anatomiques de la dyssentérie en Cochinchine*, Montpellier, L. Christin & Cie., 1864.

3. Layet: *Thèse de Montpellier*, 1872. Laveran, A.: *La diarrhée de Cochinchine*, Bull. et mém. Soc. méd. d. hôp. de Paris **14**:71, 1877.

4. Manson, Patrick: *Notes on Sprue*, Medical Report, China Imperial Maritime Customs, Shanghai, 1879-1880.

van der Burg,⁵ in Java, described the features of the disease which Hillary had observed. Each of these observers adopted as a scientific name for the disease its popular designation in Java. Since then the individuality of "sprue" has been established and its features have been described by many authors.

Various theories of the cause of the disease have been proposed. The original conflict between the theory of an infection and that of a deficiency origin has persisted. In 1884 Kiéner and Kelsch⁶ claimed that in all cases of sprue there was an initial intestinal lesion from which the infection spread. Two years later the concept of deficiency disease was suggested by Maclean,⁷ who reenforced the theory of Grant⁸ that the stomatitis and aphthae were of scorbutic origin by stating that in order to effect a cure of the disease antiscorbutic remedies were required. In 1901 Kohlbrugge⁹ gave definite impetus to the theory of an infectious origin by describing a yeast which he found in the feces as well as invading the mucous membranes of the intestinal canal. This lead was taken up by Castellani and Low,¹⁰ Ashford,¹¹ Bahr¹² and others.¹³ Ashford, working in Puerto Rico, became an enthusiastic exponent of the theory that the disease is due to a yeast, and in 1917 he described as the etiologic agent a species of *Monilia* which he claimed¹⁴ to have found consistently on the tongue and in the feces of his patients. Ashford's views were, however, subsequently modified to admit the

5. van der Burg, C. L.: *Indische Spruw (Aphthae tropicae)*, Batavia, Ernst & Company, 1880; translated in Medical Report, China Imperial Maritime Customs, Oct.-March, 1883.

6. Kiéner and Kelsch: *Étude anatomo-pathologique de la dysentérie et recherches sur les nécroses expérimentales de la muqueuse intestinale*, Arch. de physiol. norm. et path. **3**:186, 1884.

7. Maclean, W. C.: *Diseases of Tropical Climates: Lectures Delivered at the Army Medical School, London*, The Macmillan Company, 1886.

8. Grant, Alexander: *Remarks on Hill Diarrhoea and Dysentery*, Indian Ann. M. Sc. **1**:311, 1853-1854.

9. Kohlbrugge, I. H. F.: *Een bijdrage tot de aetiologie der indische spruw (psilosis)*, Nederl. tijdschr. v. geneesk. **37**:881 (Oct. 19) 1901; *Die Aetiologie der Aphthae tropicae*, Arch. f. Schiffs- u. Tropen-Hyg. **5**:394, 1901.

10. Castellani, Aldo, and Low, G. C.: *The Rôle Played by Fungi in Sprue*, J. Trop. Med. **16**:33 (Feb. 1) 1913.

11. Ashford, B. K.: *A Monilia Found in Certain Cases of Sprue: Preliminary Note*, J. A. M. A. **64**:810 (March 6) 1915.

12. Bahr, P. H.: *A Report on Researches on Sprue in Ceylon, 1912-1914*, London, Cambridge University Press, 1915.

13. (a) Le Dantec, A.: *Présence d'une levure dans le sprue: Sa signification pathogénique*, Compt. rend. Soc. de biol. **64**:1066, 1908. (b) Wood, E. J.: *Pernicious Anemia in Its Relationship to Sprue: A Preliminary Report*, Am. J. M. Sc. **169**:28 (Jan.) 1925.

14. Ashford, B. K.: *The Etiology of Sprue*, Am. J. M. Sc. **154**:157 (Aug.) 1917.

basic factor of "nutritional unbalance."¹⁵ Mackie and Chitre¹⁶ have expressed the belief that there is no evidence to show that yeasts have a causative relation to sprue, and Mackie, Goré and Wadia¹⁷ were unable to ascribe the disease to any recognized pathogenic bacteria.

The concept of sprue as a deficiency disease was again advocated in 1920 by Elders,¹⁸ partly on the basis of McCarrison's¹⁹ observations on the changes of the gastro-intestinal tract induced in experimental animals by feeding diets then considered to be deficient in vitamin B. The dietetic treatment naturally applied for the diarrhea of sprue was elaborated into a valuable regimen, but like the early dietetic treatment of scurvy or pellagra it was founded on an empiricism which suggested to very few a relationship to the cause of the disorder. In 1926 Minot and Murphy²⁰ announced a successful treatment for pernicious anemia consisting in a diet including large amounts of liver. Despite the fact that the liver extracts subsequently developed for the treatment of pernicious anemia by Cohn, Minot and their collaborators²¹ were shown to be effective in the treatment of the macrocytic anemia of sprue in certain instances by Bloomfield and Wyckoff,²² Richardson and Klumpp,²³ Ashford²⁴ and others,²⁵ this observation failed to modify

15. Ashford, B. K.: Observations on the Conception That Sprue Is a Mycosis Superimposed upon a State of Deficiency in Certain Essential Food Elements, *Am. J. Trop. Med.* **2**:139 (March) 1922.

16. Mackie, F. P., and Chitre, G. D.: (a) Yeasts and Sprue, *Indian Medical Research Memoir*, no. 11, Calcutta, Thacker, Spink & Company, 1928; (b) Animal Experiments and Sprue, *Indian J. M. Research* **16**:49 (July) 1928.

17. Mackie, F. P.; Goré, S. N., and Wadia, J. H.: The Bacteriology of Sprue, *Indian J. M. Research* **16**:95 (July) 1928.

18. Elders, C.: Over de proeven van McCarrison in verband met de opvatting, dat indische spruw een deficiëntieziekte is, *Nederl. tijdschr. v. geneesk.* **64**:2189, 1920.

19. McCarrison, Robert: *Studies in Deficiency Disease*, London, Henry Frowde & Hodder & Stoughton, 1921.

20. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* **87**:470 (Aug. 14) 1926.

21. Cohn, E. J.; Minot, G. R.; Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia, *J. Biol. Chem.* **77**:325 (May) 1928.

22. Bloomfield, A. L., and Wyckoff, H. A.: The Treatment of Sprue with Liver Extract (343), *Am. J. M. Sc.* **177**:209 (Feb.) 1929.

23. Richardson, Wyman, and Klumpp, T. G.: Sprue: Report of a Case Treated with the Authorized Liver Extract Effective in Pernicious Anemia, *New England J. Med.* **199**:215 (Aug. 2) 1928.

24. Ashford, B. K.: The Anemias of Sprue: Their Nature and Treatment, *Arch. Int. Med.* **45**:647 (May) 1930.

25. (a) Suárez, R. M.: El tratamiento del esprú y el uso del extracto acuoso de hígado en su anemia, *Bol. Asoc. méd. de Puerto Rico* **23**:74 (March) 1931. (b) Suárez, J.: Pernicious Anemia and Sprue, *Porto Rico J. Pub. Health & Trop. Med.* **7**:145 (Dec.) 1931.

greatly the customary dietary treatment of sprue. This is difficult to understand in view of the fact that in an early paper Minot and Murphy²⁶ stated that the lingual and gastro-intestinal symptoms of pernicious anemia, like the anemia, were favorably affected by liver therapy. Moreover, liver soup had already been introduced by Manson in 1883 and used in the treatment of sprue for many years before the work of Minot and Murphy, as was stated by them.

With this background, our observations on sprue were begun under the auspices of the Rockefeller Foundation in Puerto Rico in 1931. A brief report²⁷ of the results has already been published. The present detailed report takes cognizance of certain subsequent observations made on patients and animals and so brings together evidence considered to indicate that sprue is primarily a deficiency disease closely allied to Addisonian pernicious anemia and that substances present in extracts of liver effective in the treatment of pernicious anemia have a highly beneficial effect on all the major features of sprue.

METHODS

Observations were begun on over 100 patients with sprue and were satisfactorily carried out on 92. The patients were selected on the basis of symptomatology, such as sore tongue and diarrhea, or because they had definite anemia, usually of the macrocytic type. Thus, the group of patients included persons suffering both from the syndrome of "nutritional unbalance" of Ashford²⁸ and from fully developed and outspoken sprue with severe anemia. Most of the patients were adults. Patients with loss of blood or complicating infections were excluded as far as was possible. In several instances hookworm ova were found in the stools, and in a few cases the parasites were expelled at the completion of the observation. Experience with the anemia associated with hookworm infection indicated that, although the hookworm might have an influence in determining the type or degree of anemia, the results of effective therapy would not be greatly modified by their presence.²⁹

The patients were observed either in the hospital or as visitors to a special clinic established at the Presbyterian Hospital in San Juan. Three of the patients were the subjects of special studies at the Thorndike Memorial Laboratory of the Boston City Hospital. Patients under observation in the hospitals, unless otherwise specified, were given a basal diet resembling as closely as possible the usual food of the Puerto Rican peasant. The major articles of this diet were rice, shell

26. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia: Study of One Hundred and Five Cases, *J. A. M. A.* **89**:759 (Sept. 3) 1927.

27. Castle, W. B., and Rhoads, C. P.: The Aetiology and Treatment of Sprue in Porto Rico, *Lancet* **1**:1198 (June 4) 1932; Observations on the Etiology and Treatment of Sprue in Puerto Rico, *Tr. A. Am. Physicians* **47**:245, 1932.

28. Ashford, B. K.: Sprue, in Tice, Frederick: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 4, p. 173. Ashford.¹⁵

29. Rhoads, C. P.; Castle, W. B.; Payne, G. C., and Lawson, H. A.: Observations on the Etiology and Treatment of Anemia Associated with Hookworm Infection in Puerto Rico, *Medicine* **13**:317 (Sept.) 1934.

beans and white bread, such tropical vegetables as *yautia*, *ñame* and *plátano* and the juices of citrous fruit. Meat and eggs were not given. A small amount of milk was permitted in coffee. Salt and sugar were given as desired. Carbohydrate desserts with syrup were freely used. The quantity of the diet was limited only by the desire of the individual patient for food. Numerous control periods of observations showed that the symptoms and blood picture of the patients were never significantly improved by this basal regimen. In the management of outpatients suggestions as to diet were never made. Usually a general history, and in 63 instances a dietary history, was taken, and a physical examination was carried out. The blood was examined for malaria in all doubtful cases, and the Kahn test for syphilis was always performed. Biopsies of the sternal bone marrow were made on 22 patients at various stages of the anemia. Gastric analyses were performed on 65 patients. Systematic culture of the stools of 56 patients for yeastlike organisms was made and controlled with similar observations on a series of 46 patients with hypochromic anemia associated with hookworm infection.

The hematologic studies were made on 5 cc. samples of venous blood drawn without stasis and rendered incoagulable by 0.05 cc. of a 20 per cent solution of potassium oxalate. Since the factors of dilution and shrinkage of the cells were small and constant, no corrections were made for them. The corpuscular counts were made by the usual technic with certified apparatus. The percentage of hemoglobin was determined with a single Sahli instrument with a solid standard. One hundred per cent was considered equivalent to 15.6 Gm. per hundred cubic centimeters of blood. The indexes of mean corpuscular volume and of hemoglobin were calculated from uncorrected hematocrit values determined by the method of Wintrobe.³⁰ The color of the serum was estimated with bichromate standards according to the method of Murphy,³¹ and the bilirubin content of the serum was determined by the well known quantitative method of van den Bergh. Blood films were made on coverglasses previously coated with brilliant cresyl blue in order to stain the reticulocytes supravivally before the films were counterstained with Wright's stain. When a patient was in the hospital a 5 cc. sample of venous blood was usually taken every other day, and reticulocyte counts were made daily. For outpatients samples of venous blood were examined at intervals of one or two weeks.

The plan of study included the descriptive observations just mentioned and determinations under controlled conditions of the effect of various procedures, especially on the formation of blood. Previous experience with a few cases of sprue observed in Boston had suggested certain significant etiologic relationships between the anemia of sprue and that of addisonian pernicious anemia. Attempts were therefore made to evaluate the relative importance of dietary deficiency, specific changes in the gastric contents and disturbances of the absorption of hematopoietic substances. In view of the work of Bloomfield and Wyckoff,²² Ashford,²⁴ R. M. and J. Suárez²⁵ and others²³ on the effects of extracts of liver known to be potent in the treatment of pernicious anemia, studies of the therapeutic value of liver extracts administered both orally and parenterally^{31a} were carried out.

30. Wintrobe, M. M.: The Volume and Hemoglobin Content of the Red Blood Corpuscle: Simple Method of Calculation, Normal Findings, and Value of Such Calculations in the Anemias, *Am. J. M. Sc.* **177**:513 (April) 1929.

31. Murphy, W. P.: An Easy Method of Estimating the Amount of Jaundice by Means of the Blood Serum, *Boston M. & S. J.* **194**:297 (Feb. 18) 1926.

31a. Unless otherwise specified, liver extract-Lilly, N. N. R., supplied by the manufacturer, was used for oral administration. The product for parenteral use was prepared by us from this substance.

As far as can be ascertained, except for a patient previously treated³² in Boston, these were the first observations on the parenteral use of liver extract in the treatment of sprue.²⁷ The effects on the formation of blood of a dietary regimen for sprue and of preparations of autolyzed yeast were compared with those of liver extract therapy. The accessory value of iron therapy was also determined.

The immediate effect of these procedures on the formation of blood was determined by daily observations of the course taken by the reticulocyte count. This index has been applied to the study of both macrocytic and hypochromic anemia.³³ It permits the detection of hematopoietic activity within from ten to fourteen days and affords a basis of comparison in the same patient of the hematopoietic effects of different substances. The principles of this test in pernicious anemia have recently been reviewed by Minot.³⁴ Here it suffices to say that from the uniform daily administration of hematopoietically active substances to patients with less than 3,000,000 red blood cells per cubic millimeter an increase in the reticulocyte count may be expected to appear before the tenth day and reach a "peak" value usually about the seventh day, rarely as late as the fourteenth day, after the initiation of therapy. The peak value is roughly proportional to the amount of active substance administered up to a given maximal dosage of the active material. The peak value of the reticulocyte count is also roughly inversely proportional to the initial level of the erythrocyte count. If in response to the uniform daily administration of an active substance a submaximal reticulocyte value has occurred and is on a decline, the immediately subsequent uniform daily administration of a larger amount of active material may produce a second peak of the reticulocyte count higher than, equal to, or lower than, the first. The relative magnitude of the second peak will depend on how much greater than the activity of the first material was the activity of the second material administered. On these principles are based many of the observations on the patients with sprue to be described later. In addition, the effect of certain procedures on the values for red blood cells and hemoglobin was determined.

OBSERVATIONS CONCERNING THE ETIOLOGY OF SPRUE

DESCRIPTIVE OBSERVATIONS

Excellent descriptions of sprue have been recorded by clinicians whose experience has been far more extended than ours. The following

32. Strauss, M. B., and Castle, W. B.: Parenteral Liver Therapy in the Treatment of Pernicious Anemia, *J. A. M. A.* **98**:1620 (May 7) 1932.

33. (a) Minot, G. R.; Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy, Particularly in Pernicious Anemia, *Am. J. M. Sc.* **175**:581 (May) 1928. (b) Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract: Effects upon the Production of Immature and Mature Red Blood Cells, *ibid.* **175**:599 (May) 1928. (c) Bethell, F. H., and Goldhamer, S. M.: Standards for Maximum Reticulocyte Values Following Ventriculin and Intravenous Liver Extract Therapy in Pernicious Anemia, *ibid.* **186**:480 (Oct.) 1933. (d) Minot, G. R., and Heath, C. W.: The Response of the Reticulocytes to Iron, *ibid.* **183**:110 (Jan.) 1932.

34. Minot, G. R.: The Interpretation of Reticulocyte Responses in Pernicious Anemia, *Tr. A. Am. Physicians* **49**:287, 1934. Minot, G. R., and Castle, W. B.: The Interpretation of Reticulocyte Reactions: Their Value in Determining the Potency of Therapeutic Materials, Especially in Pernicious Anemia, *Lancet* **2**:319 (Aug. 10) 1935.

descriptions of the clinical features, the blood picture and the bone marrow in cases of sprue, however, may be of value because presented by observers to whom, although the clinical study of sprue was essentially new, other types of severe anemia were familiar. A deliberate attempt was therefore made not to become involved in a study of the minute details of the clinical picture so well done by others. Rather, it was our object to compare the chief manifestations of sprue with the corresponding features of other diseases with gastro-intestinal symptoms and signs in which anemia is a common finding.

The Clinical Picture.—In his classic description of sprue Manson³⁵ divided the patients into two groups: those with “complete” and those with “incomplete” sprue. The latter designation was applied to those patients in whom there were no symptoms referable to the tongue and mouth and in whom intestinal symptoms predominated. In 1915 Bahr¹² added a third division of the cases by including patients suffering from “tongue or mouth” sprue. In these patients symptoms referable to the tongue and mouth may be present for years without other features of the fully developed disease. Ashford²⁸ apparently classified under his syndrome of “nutritional unbalance preceding sprue” the groups of incomplete and tongue-and-mouth sprue. His vivid description of this state was based on years of observation. It apparently corresponds to the condition of only about 16 of our 92 patients. In a recent article Manson-Bahr and Willoughby³⁶ classified 22 per cent of their 200 cases under incomplete sprue. Since it was our object to examine patients mainly with the fully developed disease and anemia or patients who presented definite lingual changes, many patients with suspicious early sprue of this type were not admitted for study. It is our impression that the asthenia, sore and “inflamed” tongue, copious foamy stools and emaciation were stages of variable duration of a disorder of an irregularly progressive character. The symptoms of the incomplete disease were often those which had been presented for a short time by the patient with fully developed sprue. For this reason the dynamic rather than the static picture of the symptomatology is, as implied by Ashford,²⁸ essential to a depiction of the disease.

Certain writers have noted the occurrence of symptoms and signs suggestive of neurologic involvement in sprue clinically³⁷ and at post-

35. Manson, Patrick: Sprue, in Allbutt, C., and Rolleston, H. D.: *A System of Medicine*, New York, The Macmillan Company 1907, vol. 2, p. 545. Manson.⁴

36. Manson-Bahr, Philip, and Willoughby, Hugh: *Studies on Sprue with Special Reference to Treatment: Based upon an Analysis of Two Hundred Cases*, Quart. J. Med. **23**:411, 1930.

37. (a) Hance, J. B.: Notes on the Pathogenesis of Sprue and the Asthenic Diarrhoea of Indians, Indian M. Gaz. **65**:125 (March) 1930. (b) Baumgartner, E. A., and Smith, G. D.: Pernicious Anemia and Tropical Sprue, Arch. Int. Med. **40**:203 (Aug.) 1927. (c) Wood.^{13b}

mortem examination.³⁸ Suspicious signs of mild forms of this condition were observed in 8 of the 92 patients of this series. The symptoms are not to be confused with the frequent and inconstant cramps of the muscles or transitory numbness and coldness of the hands and feet. These patients exhibited a definite instability of locomotion and complained of constant symmetrical paresthesia in the hands or feet. Some diminution of the sense of vibration of the ankles was present in all; in 3 patients the knee jerks were greatly diminished, but in none was the Babinski phenomenon present. Aside from this our observations of the clinical features of the cases studied in Puerto Rico bear out the excellent recent clinical descriptions of Manson,³⁵ Ashford,²⁸ the Bahrs,³⁹ Baumgartner^{37b} and others.⁴⁰

The Blood Picture.—The blood picture in sprue has frequently been described and the resemblance of the macrocytic anemia to pernicious anemia pointed out.⁴¹ Ashford²⁸ found that about half of his severely anemic patients in Puerto Rico showed a "secondary" type of anemia. Fairley, Mackie and Billimoria⁴² found that over half of their 67 patients had a color index of 1 or more. Baumgartner⁴³ stated that of 36 patients 16 had anemia with a high color index. All these authors have emphasized the large size of the red cells as measured by the technic of Price-Jones⁴⁴ in those patients whose blood showed a high color index. They have agreed that the white blood cells have a tendency to be decreased in numbers with relative lymphocytosis in the patients with the lower red blood cell counts. Baumgartner found the Arneth count of value in distinguishing the anemia of sprue from that of pernicious anemia since the lobulations of the neutrophils in a person with sprue resemble more nearly those in the blood of a normal person. Few observations of the platelets have been recorded. Fairley, Mackie and Billimoria found that the bilirubin content of the blood was not increased so constantly as in cases of pernicious anemia with relapse. Otherwise the blood picture found by these authors in many instances appears to be indistinguishable from that of pernicious anemia.

38. Reed, A. C., and Wyckoff, H. A.: The Common Picture of Sprue, Pernicious Anemia, and Combined Degerenation, *Am. J. Trop. Med.* **6**:221 (May) 1926.

39. Manson-Bahr and Willoughby.³⁶ Bahr.¹²

40. Musser, J. H.: Clinical Manifestations of Sprue and Relation of the Disease to Pernicious Anemia, *M. Clin. North America* **9**:895 (Jan.) 1926.

41. Reed and Wyckoff.³⁸ Musser.⁴⁰ Wood.^{13b}

42. Fairley, N. H.; Mackie, F. P., and Billimoria, H. S.: Anaemia in Sprue: An Analysis of Sixty-Seven Cases, *Indian J. M. Research* **16**:831 (Jan.) 1929.

43. Baumgartner, E. A.: The Blood Picture in Tropical Sprue, *Folia haemat.* **43**:192, 1930.

44. Price-Jones, Cecil: The Diurnal Variation in the Sizes of Red Blood Cells, *J. Path. & Bact.* **23**:371, 1920.

The findings in the blood of our series of 92 patients are perhaps not comparable to those of other observers since the patients were especially selected for study because they had severe anemia of the macrocytic type. Ashford⁴⁵ has reported the occurrence of lingual and gastrointestinal symptoms in patients regarded as suffering from hookworm disease. Such symptoms were frequently observed in our series of patients with hypochromic anemia and hookworm infection.²⁹ These similarities indicate the difficulty of distinguishing, on a symptomatic basis, certain patients with hookworm disease from others with sprue. Conversely, several of the patients here included as having sprue were carriers of the hookworm, although most of them did not have the hypochromic type of anemia usually associated with infection with that parasite. With these reservations, the individual blood pictures on the first examinations of our 92 patients regarded as suffering from sprue are set forth in table 1 and are summarized in table 2 with respect to initial values of red blood cells, white blood cells, color index, mean corpuscular volume, mean concentration of corpuscular hemoglobin and icterus index. With the particular technic employed the average indexes for cell volume and concentration of hemoglobin of Wintrobe³⁰ determined on four different occasions on 5 normal subjects were: for mean corpuscular volume, 84.8 cubic microns, and for mean concentration of corpuscular hemoglobin, 34.3 per cent. Because these figures were uncorrected for cell shrinkage they vary slightly from the average corrected values given by Wintrobe.

In general the blood picture was that of macrocytic anemia, although in cases 11, 28, 29, 41, 84 and 87 the picture assumed a definitely hypochromic character and in cases 11 and 87 it was also microcytic. In cases 28 and 84 hookworm ova were found in the stools. Marked variation in the size and shape of the erythrocytes, with many oval cells and occasional primitive nucleated cells, was noted in severely anemic patients. Leukopenia, often with relative lymphocytosis, and diminution of the blood platelets were noted in stained films. These observations confirm those of others and show that the blood picture is similar to that of addisonian pernicious anemia.

The blood picture of sprue, however, has been stated to differ from that of pernicious anemia in that the anemia in the latter condition is more regularly macrocytic⁴⁶ and the frequency of an elevated content of serum bilirubin greater.⁴² In table 2 are summarized the major features of the initial blood findings in the 92 patients with sprue as compared with the findings in 40 patients with pernicious anemia, mainly in the first relapse, who were admitted consecutively to the Harvard medical

45. Ashford, B. K.; King, W. W., and Gutiérrez Igaravidez, P.: Report of the Study and Treatment of "Anemia" in Porto Rico, San Juan, Puerto Rico, Bureau of Printing and Supplies, 1904.

46. Ashford.²⁸ Baumgartner.⁴³

TABLE 1.—The Initial Blood Findings, Duration and Type of Symptoms, Results of Gastric Analysis and Observations for Yeastlike Organisms and Hookworm Ova in the Stools of 92 Patients with Sprue

Case	Sex	Age, Years	Red Blood Cells, Millions	Hemo- globin, per Cent	White Blood Cells, Thou- sands	Reticulo- cytes, per Cent	Color Index	Mean Corpus- cular Volume, Cubic Microns	Mean Con- centra- tion of Corpus- cular Hemo- globin, per Cent	Icterus Index	Symptoms			Gastric Analysis*	Stools	
											Dura- tion	Tongue, rhea	Nerve		Posti- tive	Yeast Cultures
1	M	46	3.52	78	3.3	0.4	1.10	110	31	4	5 yr.	+	0	+	..	0
2	F	25	1.56	32	4.8	3.4	1.02	108	30	2	9 mo.	+	0	hist.	..	12
3	F	56	3.73	78	3.5	1.0	1.04	99	33	..	2 yr.	+	0	ale.	2	0
4	M	55	2.26	55	5.6	3.2	1.22	125	30	2	+	0	ale.	1	117
5	M	22	1.56	44	6.2	1.4	1.82	136	32	3	3 mo.	+	0	ale.	2	0
6	M	53	1.92	47	5.7	1.2	1.22	118	32	7	0
7	F	55	3.60	82	8.7	1.6	1.14	104	34	3
8	F	63	1.22	32	2.9	0.8	1.31	120	34	12	4 yr.	+	0	hist.	5	0
9	F	47	2.15	55	6.7	1.4	1.27	123	31	3	10 mo.	+	0	hist.	1	0
10	M	29	2.39	67	3.0	1.0	1.40	129	34	3	15 yr.	+	0	ale.	3	0
11	F	33	4.66	50	10.4	2.2	0.54	61	27	2	5 yr.	+	0	2	0
12	F	41	2.20	64	7.1	0.5	1.45	137	33	2	18 mo.	+	0	hist.	2	0
13	M	60	2.67	65	6.7	...	1.22	114	33	3	+
14	M	45	2.46	60	5.6	0.8	1.22	114	33	6	2 yr.	+	0	ale.	5	0
15	M	60	1.80	50	7.8	4.2	1.39	135	32	5	10 yr.	+	..	hist.	3	0
16	F	40	1.94	43	5.6	1.0	1.11	112	31	4	+	..	ale.	1	0
17	F	12	2.56	75	3.6	1.2	1.46	127	36	4	4 yr.	+	0	0
18	M	48	2.80	71	3.5	0.8	1.27	114	35	8	1 yr.	+	0	0	1	0
19	M	48	1.55	36	4.6	0.6	1.16	111	33	3	4 yr.	+	0	0	..	+
20	M	35	2.67	68	7.1	1.2	1.27	120	33	5	4 yr.	+	0	0	..	0
21	M	49	2.30	70	3.8	1.2	1.52	145	33	2	2 yr.	+	0	hist.	1	..
22	M	69	1.98	56	5.6	0.8	1.41	140	31	2	1 mo.	+	0	0	4	..
23	M	68	1.63	42	8.5	1.8	1.29	132	31	8	3½ yr.	+	0	ale.	1	..
24	F	51	2.67	54	8.5	1.0	1.01	110	29	3	+	0	0
25	M	42	2.51	78	4.8	1.6	1.55	141	35	3	+	0
26	F	44	3.18	64	2.2	0.4	1.00	105	30	4	4 yr.	+	0	ale.	1	0
27	F	59	1.39	48	3.9	0.6	1.27	166	32	6	12 yr.	+	0
28	M	30	0.83	14	2.5	3.6	0.84	92	29	4	8 mo.	+	0	ale.	1	536 worms
29	M	63	3.68	67	4.2	0.4	0.91	90	32	3	4 mo.	+	0	hist.	1	..
30	F	60	1.30	33	3.8	2.4	1.27	132	30	6	3 mo.	+	0	0	4	7
31	M	20	1.28	49	2.1	4.0	1.91	154	39	30	8 yr.	+	0	0	1	328
32	F	72	1.23	31	4.2	0.8	1.26	120	33	30	2 yr.	+	0	ale.	1	0
33	F	66	1.48	45	3.5	1.4	1.32	153	31	3	2 yr.	+	0
34	F	65	2.33	57	4.5	4.8	1.22	113	34	3	+	0	ale.	3	0
35	M	65	1.76	49	2.4	0.8	1.39	132	33	6	10 yr.	+	0	0	2	23
36	M	22	1.94	45	4.5	3.0	1.16	111	33	5	10 yr.	+	0	ale.	..	0
37	M	67	1.92	42	4.0	1.4	1.09	104	33	3	2 yr.	+	0	0	2	0
38	F	35	3.11	75	6.2	1.2	1.20	119	38	3	+	0	ale.	1	1
39	M	58	2.00	58	4.5	0.8	1.45	141	32	4	7 yr.	+	0	0	..	0
40	M	62	1.54	47	5.0	3.6	1.53	133	36	3	5 yr.	+	0	hist.	..	0

services of the Boston City Hospital during the past two years. It is clear that the resemblances between the blood findings of the two groups are striking. The patients with pernicious anemia had, on the average, a greater degree both of anemia and of leukopenia. The mean concentration of corpuscular hemoglobin was more than 34 per cent in a greater percentage of the patients with pernicious anemia. On the other hand, the percentage of patients with a color index greater than

TABLE 2.—*Comparison of Initial Blood Values of 92 Patients with Sprue with Those of 40 Patients with Addisonian Pernicious Anemia**

	Erythrocytes, Millions per Cu. Min.				
	0 to 0.9	1 to 1.99	2 to 2.99	3 to 3.99	4 to 4.99
Sprue.....	9.8	41.3	33.7	14.1	1.1
Pernicious anemia.....	7.5	62.5	25.0	5.0	0

	Leukocytes, Thousands per Cu. Mm.			
	<3	3 to 4.9	5 to 6.9	>7
Sprue.....	18.5	42.4	23.9	15.2
Pernicious anemia.....	35.0	47.5	15.0	2.5

	Color Index						
	<0.6	0.6 to 0.79	0.8 to 0.99	1 to 1.19	1.2 to 1.39	1.4 to 1.59	>1.6
Sprue.....	2.2	0	4.4	21.7	38.0	28.3	5.4
Pernicious anemia.....	0	0	5.0	40.0	50.0	2.5	2.5

	Mean Corpuscular Volume, Cubic Microns (Normal, 84.8)								
	<80	80 to 89	90 to 99	100 to 109	110 to 119	120 to 129	130 to 139	140 to 149	>150
Sprue.....	2.2	1.1	6.6	12.1	21.9	18.7	16.5	12.1	8.8
Pernicious anemia...	0	2.5	10.0	32.5	22.5	25.0	7.5	0	0

	Mean Concentration of Corpuscular Hemoglobin, Percentage (Normal, 34.3)							
	<29	29	30	31	32	33	34	>34
Sprue.....	2.2	2.2	7.7	9.9	15.4	27.4	15.4	19.8
Pernicious anemia.....	0	7.5	5.0	7.5	15.0	10.0	20.0	35.0

	Icterus Index, Units (Normal, 6)		
	<6	6 to 10	>10
Sprue.....	58.0	22.7	19.3
Pernicious anemia.....	46.7	40.0	13.3

* The figures in the table indicate the percentage distribution.

1.4 was larger in the group with sprue, as was the percentage of patients with a mean corpuscular volume over 130 cubic microns. Finally, an icterus index³¹ above the normal value of 6 units was found almost as often in the patients with sprue as in those suffering from pernicious anemia. Values for the icterus index over 10 units were actually found in a greater percentage of the patients with sprue. It is thus difficult to discover in this comparison by identical technics of the morphologic

characteristics of the blood in the two conditions any consistent diagnostic criteria for differentiation of the diseases. The possible differential value of the Arneht count⁴³ was not studied.

The Bone Marrow.—Mackie and Fairley⁴⁷ described the changes in the femoral and tibial bone marrow of a group of patients with sprue who came to autopsy. They observed in different patients instances of hyperplastic marrow such as is found in patients with pernicious anemia, fatty marrow with circumscribed areas of activity and marrow showing gelatinous degeneration. Ashford⁴⁸ found both hyperplastic and aplastic histologic pictures in specimens of tibial marrow removed during life. Krjukoff⁴⁹ made detailed studies of the marrow obtained for biopsy from the ribs of 16 patients with sprue. He found uniformly a megaloblastic change of the marrow. Since Peabody,⁵⁰ in connection with a study of the tibial bone marrow in cases of pernicious anemia, has emphasized the fact that the marrow of a long bone such as the tibia does not necessarily reflect the changes in the marrow of those bones normally containing active cellular marrow in adult life, these discrepancies are easily understood. Our observations, based on biopsy specimens of sternal marrow of 22 patients with sprue and anemia of a macrocytic type, have been reported in detail elsewhere.⁵¹ The specimens obtained showed that in untreated patients with severe anemia the essential change is a proliferation of megaloblasts with suppression of maturation beyond this stage. During remissions induced with liver therapy the marrow tends to return to normal through a transitional stage in which are seen large numbers of normoblasts. Phagocytosed erythrocytes were observed in the specimens of marrow removed at autopsy but not in those removed during life. The cellular changes in the normally active marrow in different stages of the disease were thus similar to those observed in cases of pernicious anemia by Peabody.⁵⁰ Judging from the results of others it is probable, however, that hyperplastic marrow in the long bones is not so regularly found or so extensive as in cases of pernicious anemia. A summary of the histologic observations on bone marrow, including changes with therapy, is shown in table 3.

47. Mackie, F. P., and Fairley, N. H.: *The Morbid Anatomy of Sprue*, Indian J. M. Research **16**:799 (Jan.) 1929.

48. Ashford, B. K.: *The Differential Diagnosis of Sprue and Pernicious Anemia*, Am. J. Trop. Med. **12**:199 (May) 1932.

49. Krjukoff, A.: *Anämie bei Sprue*, Folia haemat. **35**:329 (Jan.) 1928.

50. Peabody, F. W.: *The Pathology of the Bone Marrow in Pernicious Anemia*, Am. J. Path. **3**:179 (May) 1927.

51. Rhoads, C. P., and Castle, W. B.: *The Pathology of the Bone Marrow in Sprue Anemia*, Am. J. Path. **9**:813, 1933.

TABLE 3.—Blood Picture and Observations on the Bone Marrow in Patients with Anemia of Sprue*

Case	Blood Picture				Bone Marrow				Fat	Comment			
	Red Blood Cells, per Millions	Hemo- globin, per Cent	White Cells, Thous- ands	Mean Cor- puscular Volume, per Cent	Icterus Index	Color Index	Biopsy or Autopsy	Source of Marrow			Untreated Patients		
											General Cellularity	Erythro- blasts	Normo- blasts
9	2.15	54	8.1	1.8	130	2	1.25	Biopsy	Sternum	++	++	++	Early though definite megaloblastic preponderance
15	1.76	49	6.2	1.4	126	5	1.39	Biopsy	Sternum	+++	+	+	Moderate megaloblastic proliferation and preponderance
30	1.41	40	3.3	3.2	126	4	1.42	Biopsy	Sternum	+++	+	—	Intense megaloblastic proliferation and preponderance
31	1.42	48	2.2	6.6	140	40	1.69	Biopsy	Sternum	+++	+	—	
32	0.98	28	2.2	0.8	143	25	1.43	Biopsy	Sternum	+++	+	—	
34	2.51	53	3.3	4.8	101	2	1.10	Biopsy	Sternum	+++	+	—	
36	1.96	46	9.8	1.4	114	2	1.17	Biopsy	Sternum	+++	+	—	
37	1.92	42	4.8	2.0	102	5	1.10	Biopsy	Sternum	+++	+	—	
39	2.07	66	7.4	2.2	119	3	1.24	Biopsy	Sternum	+++	+	—	
53	1.15	34	5.1	3.8	131	30	1.48	Biopsy	Sternum	+++	+	—	
58	2.52	63	8.1	3.2	128	3	1.25	Biopsy	Sternum	+++	+	—	
60	3.12	73	7.5	1.6	107	2	1.14	Biopsy	Sternum	+++	+	—	
64	1.25	29	1.8	1.0	104	18	1.10	Biopsy	Sternum	+++	+	—	
68	1.68	55	5.0	4.6	134	5	1.63	Biopsy	Sternum	+++	+	—	
86	2.40	54	1.9	0.4	113	40	1.12	Biopsy	Sternum	+++	+	—	
79	1.46	40	3.0	0.1	121	5	1.37	Biopsy	Sternum	+++	+	+	Moderate megaloblastic proliferation and preponderance
70	1.05	29	2.9	8.8	157	12	1.38	Post-mortem	Sternum and femur	+++	—	—	Phagocytosis of red blood cells present
77	2.86	68	7.6	1.6	119	3	1.19	Post-mortem	Sternum and femur	+++	—	—	Sternal marrow red, femoral marrow partly red; lung abscess; microscopically, very loose structure
81	0.97	19	7.3	4.5	103	30	0.98	Post-mortem	Sternum and femur	+++	—	—	Brick-red marrow in sternum and upper third of femur; transfusion; microscopic structure confused; phagocytosed red blood cells
51	0.94	10	3.6	4.4	115	10	1.00	1st biopsy	Sternum	++++	+	—	Before remission; many megaloblasts, few normoblasts, almost no fat cells
51	2.97	60	3.3	4.2	100	2	1.01	2d biopsy	Sternum	++	+++	++	20 days after intramuscular injection of liver extract; normoblasts predominant
82	0.83	26	3.0	14.0	162	3	1.57	Biopsy	Sternum	++	+	+	9th day of oral administration of liver extract; during reticulocyte rise: megaloblasts separating into clumps; normoblasts appearing
75	1.40	29	2.3	21.6	114	6	1.04	1st biopsy	Sternum	+++	++	+	9 days after intramuscular injection of liver extract; during reticulocyte rise: decrease in megaloblasts; increase in normoblasts
75	2.69	55	2.8	2.0	99	2	1.02	2d biopsy	Sternum	+	++++	++	30 days after administration of liver extract; late remission: picture in marrow approaches normal except for increased normoblasts

* TRANSFUSIONS TO THE MARROW, WITH MODIFICATIONS, AS FIRST USED BY AN OTHER SECTION OF THE CHICAGO AND COASTAL HOSPITALS.

PHYSIOLOGIC OBSERVATIONS

Resemblance of Sprue to Pellagra and Pernicious Anemia.—In each of the diseases, pernicious anemia, pellagra and sprue, disturbances of the gastro-intestinal tract, of the formation of blood and of the central nervous system are associated.⁵² In general, in each disease, however, the incidence and degree of disturbance of the three systems of the body differ; and in different persons with each disease the extent of the involvement of any of the three systems is variable. Thus, in over half the cases of pernicious anemia glossitis and digestive disturbances occur, in cases of pellagra these symptoms are probably more constant, and in cases of sprue the diagnosis is almost impossible in their absence. In all three diseases the symptoms and signs relative to the tongue are similar, although in pellagra and in sprue the disturbance is more marked. In all three diseases anemia of the macrocytic type may occur, although it is not so common or so severe in pellagra as in the other two. In none of these conditions is macrocytic anemia invariable, and the development of hypochromic anemia has been reported in each.⁵³ In many cases of pernicious anemia definite evidence of disturbance of the central nervous system is present. In cases of pellagra mental symptoms, which are sometimes observed in association with pernicious anemia, are more common than is evidence of subacute combined degeneration of the spinal cord. The mental symptoms of sprue, though frequent, are usually not so pronounced as those of pellagra but are perhaps more marked than those of pernicious anemia. Neurologic involvement is by no means as common in sprue as in pernicious anemia or pellagra, but its occasional occurrence has not escaped the notice of some observers and was suggested by the symptoms and signs presented by 8 of our 92 patients.

Many of these comparisons have been made by others. The similarities of the blood picture in pernicious anemia and in sprue have been pointed out by Elders,⁵⁴ Wood,^{13b} Baumgartner,^{37b} Ashford,²⁸ Fairley,⁴² Manson-Bahr³⁶ and others.⁵⁵ The similarities of the gastro-intestinal

52. (a) Krjukoff, A.: Die Differentialdiagnose von Addison-Biermerscher Anämie, Sprue und Pellagra, *Folia haemat.* **45**:188 (Sept.) 1931. (b) Rhoads, C. P., and Miller, D. K.: The Production in Dogs of Chronic Black Tongue with Anemia, *J. Exper. Med.* **58**:585 (Nov.) 1933. Minot and Murphy.²⁶

53. Faber, Knud, and Gram, H. C.: Relations Between Gastric Achylia and Simple and Pernicious Anemia, *Arch. Int. Med.* **34**:658 (Nov.) 1924. Krjukoff, A.: Blut und Blutbildung bei schweren Fällen von Pellagra, *Folia haemat.* **45**:196 (Sept.) 1931. Ashford.²⁸

54. Elders, C.: Tropical Sprue and Pernicious Anaemia: Aetiology and Treatment, *Lancet* **1**:75 (Jan. 10) 1925.

55. Christian, H. A.: The Achlorhydria Family Tree of Diseases, *North-west Med.* **24**:531 (Nov.) 1925. Musser.⁴⁰

disturbance in pellagra and in sprue have been remarked by Wood^{13b} and Krjukoff.^{52a} Neurologic signs³⁷ and degenerative changes³⁸ in the spinal cord in sprue resembling those in pernicious anemia and pellagra have been noted. The cutaneous lesions of pellagra thus remain the outstanding differentiating feature of this disease. It is interesting, however, that pigmentary changes of the exposed surfaces of the body have been noted both in sprue⁵⁶ and in pernicious anemia.⁵⁷

For each of these three conditions there has been developed a method of treatment based on a dietary regimen including milk and meat. Before the discovery of liver therapy for pernicious anemia the success of the regimen was distinctly greater in sprue and in pellagra than in pernicious anemia, in which, at best, treatment with a diet high in protein could be described as a palliative measure. In certain instances, however, it was somewhat successful⁵⁸ in prolonging the life of the patient. In the treatment of sprue, as an adjunct to the diet the use of liver has been of long standing, although its efficacy has been hard to judge. The original observations of Minot and Murphy²⁶ on liver therapy in pernicious anemia demonstrated an improvement, not only of the anemia, but also of the lingual and gastro-intestinal manifestations and of the symptoms in the spinal cord. Subsequent work by Cohn, Minot and their associates²¹ demonstrated the specific effectiveness of certain fractions of liver, thereafter confirmed by many others. The beneficial action of such liver extracts on the disturbances in the alimentary tract⁵⁹ and anemia⁶⁰ of pellagra and on the anemia in certain cases of sprue⁶¹ has since been demonstrated. The improvement of symptoms suggestive of lesions of the cord in a few patients with sprue was observed by us to follow therapy with liver extract administered parenterally, as described later. This therapy also produced prompt improvement of the symptoms of the alimentary tract and of the macrocytic anemia of sprue. Since pellagra and pernicious anemia can almost certainly be regarded as deficiency diseases, these similarities alone are suggestive evidence of the validity of a like supposition in respect to sprue.

56. Ashford.²⁸ Manson-Bahr and Willoughby.³⁶

57. Minot, G. R.: *Diseases of the Blood: Clinical Discussion of the Anemias*, in *Oxford Medicine*, New York, Oxford University Press, 1932, vol. 2, p. 589.

58. Barker, L. F., and Sprunt, T. P.: *The Treatment of Some Cases of So-Called "Pernicious" Anemia: A Regimen That Has Been Found Helpful*, *J. A. M. A.* **69**:1919 (Dec. 8) 1917. Elders.⁵⁴

59. Ruffin, J. M., and Smith, D. T.: *The Treatment of Pellagra with Certain Preparations of Liver*, *Am. J. M. Sc.* **187**:512 (April) 1934. Spies, T. D.: *Treatment of Pellagra by Means of Parenteral Liver Extract*, *Proc. Soc. Exper. Biol. & Med.* **31**:363 (Dec.) 1933.

60. Strauss, M. B., and Castle, W. B.: Unpublished observations.

61. Bloomfield and Wyckoff.²² Richardson and Klumpp.²³ Ashford.²⁴

Analogies between the Mechanisms of Deficiency in Pernicious Anemia and Sprue.—The resemblances between the clinical picture and therapeutic response to orally administered liver extracts of patients with pernicious anemia and those of certain patients with sprue have already been summarized. Recent observations appear to demonstrate the nature of the immediate physiologic defects in pernicious anemia leading to a deficiency of "liver extract" in the body. In view of the relatively considerable knowledge of pernicious anemia and its nature, an attempt was made to discover to what extent the etiologic factors already displayed in this disease were present in sprue. Failure of the formation of blood in persons with addisonian pernicious anemia has been demonstrated⁶² to be due in large part to the absence of a specific reaction which in the normal person takes place as a result of the presence in the gastro-intestinal tract of a factor in the food (extrinsic) and a factor in the gastric juice (intrinsic). Wills⁶³ found that autolyzed yeast and liver extract were about equally effective in the treatment of macrocytic anemia of pregnancy in India. Stimulated partly by the suggestions afforded by this work, Strauss and Castle have recently shown that the food factor involved in pernicious anemia is present in autolyzed yeast⁶⁴ and is associated with a number of sources of vitamin B₂ (G).⁶⁵ So

62: (a) Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, *Am. J. M. Sc.* **178**:748 (Dec.) 1929. (b) Castle, W. B.; Heath, C. W., and Strauss, M. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: IV. A Biologic Assay of the Gastric Secretion of Patients with Pernicious Anemia Having Free Hydrochloric Acid and That of Patients Without Anemia or With Hypochromic Anemia Having No Free Hydrochloric Acid, and of the Rôle of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia, *ibid.* **182**:741 (Dec.) 1931. (c) Wilkinson, J. F.: Pernicious Anaemia: Preliminary Report on the Results Obtained by Treatment with Certain Preparations of Stomach, *Brit. M. J.* **1**:236 (Feb. 8) 1930. (d) Middleton, W. S., and Stiehm, R. H.: The Influence of Gastric Juice on Erythropoiesis in Pernicious Anemia, *Am. J. M. Sc.* **180**:809 (Dec.) 1930. (e) Helmer, O. M.; Fouts, P. J., and Zerfas, L. G.: The Relationship of the Intrinsic Factor to a Hematopoietic Material in Concentrated Human Gastric Juice, *ibid.* **188**:184 (Aug.) 1934.

63. Wills, Lucy: Treatment of "Pernicious Anaemia of Pregnancy" and "Tropical Anaemia" with Special Reference to Yeast Extract as a Curative Agent, *Brit. M. J.* **1**:1059 (June 20) 1931.

64. Strauss, M. B., and Castle, W. B.: The Nature of the Extrinsic Factor of the Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias: Activation of Yeast Derivatives with Normal Human Gastric Juice, *New England J. Med.* **207**:55 (July 14) 1932; *Lancet* **2**:111 (July 16) 1932.

65. (a) Castle, W. B.: The Etiology of Pernicious Anemia and Related Macrocytic Anemias, *Ann. Int. Med.* **7**:2 (July) 1933. (b) Singer, Karl: Eiertherapie der perniziösen Anämie, *Wien. klin. Wchnschr.* **45**:1063 (Aug. 25) 1932.

far, however, the food factor has not been identified with any portion of the vitamin B complex.⁶⁶ These principles apply as well to the etiology of macrocytic anemia of pregnancy, according to the studies of Strauss and Castle.⁶⁷ In 1931 Castle and Taylor⁶⁸ discovered that a preparation of liver suitable for parenteral use could readily be made from an already existing extract of liver (fraction G of Cohn and his co-workers) previously used only for oral administration. Since occasional patients with pernicious anemia showed relatively little response to the oral administration of the usual amounts of fraction G, but responded characteristically to parenteral injections of the same material, the suggestion was made that difficulty in the absorption of blood-forming substances from the intestinal tract was involved in these particular patients.^{62b} As a result of these observations it appeared reasonable to suppose that at least three mechanisms might be involved in the etiology of pernicious anemia or of the macrocytic anemia of patients responding characteristically to certain liver extracts. First, the food factor might be deficient; second, the gastric factor might be lacking or, third, the normal degree of intestinal absorption might be decreased. It is also clear that different combinations of these defects could produce the same end-result. The possible influence of these etiologic mechanisms in the production of sprue was accordingly investigated.

Observations on Patients with Incomplete Sprue.—In order to eliminate the secondary influence of the diarrhea and other chronic manifestations of the disease, it was considered of paramount importance to discover the factors operative at the onset of the disorder. For this reason patients were selected who were considered to have incomplete sprue, or the "syndrome of nutritional unbalance preceding sprue" of Ashford.⁶⁹ Because the degree of anemia of many of these patients

66. Wills, Lucy, and Naish, Alice: A Case of Pernicious Anaemia Treated with Vitamin B₂ from Egg White, *Lancet* **1**:1286 (June 17) 1933. Wills, Lucy: The Nature of the Haemopoietic Factor in Marmite, *ibid.* **1**:1283 (June 17) 1933. Diehl, F., and Kühnau, J.: Ist Vitamin B₂ der therapeutisch wirksame äussere Faktor beim Morbus Biermer? *Deutsches Arch. f. klin. Med.* **176**:149 (Dec.) 1933. Miller, D. K., and Rhoads, C. P.: The Presence in Egg-White and in a Rice-Polishings Concentrate Low in Vitamin B₂ (G) of an Anti-Pernicious Anemia Principle, *New England J. Med.* **211**:921 (Nov. 15) 1934.

67. Strauss, M. B., and Castle, W. B.: Studies of Anemia in Pregnancy: III. The Etiologic Relationship of Gastric Secretory Defects and Dietary Deficiency to the Hypochromic and Macrocytic (Pernicious) Anemias of Pregnancy and the Treatment of These Conditions, *Am. J. M. Sc.* **185**:539 (April) 1933.

68. Castle, W. B., and Taylor, F. H. L.: Intravenous Use of Extract of Liver: Maximal Responses of Reticulocytes from a Single Injection Derived from One Hundred Grams of Liver: Preliminary Communication, *J. A. M. A.* **96**:1198 (April 11) 1931.

69. Ashford.^{15, 28}

was slight, studies of the hematopoietic effects of various procedures were impossible. A solution of the difficulty was offered, however, by the suggestion of Rhoads that the tongue be used as an index of therapeutic effects. Although observers in Puerto Rico, among them Ashford²⁴ and Suárez,^{25b} seem not to have commented on the effect of liver extracts or of stomach preparations⁷⁰ on the lingual symptoms of sprue, the observations of Minot and Murphy,²⁶ Middleton and his associates⁷¹ and others on pernicious anemia have demonstrated the coincidence of lingual and hematologic improvement in that disease. Several years ago Manson³⁵ suggested a study of the tongue in cases of sprue because it reflected the changes in the intestinal tract. The propriety of adopting improvement in the appearance of this organ as an index of improvement of sprue was soon made clear by observations on severely anemic patients. Decrease of the symptoms and signs referable to the tongue invariably and promptly followed the injection of hematopoietically effective doses of liver extract. Observations were therefore next made on the effects of the liver extract on the lingual and gastro-intestinal phenomena of 11 patients with either early sprue or sprue with only moderate anemia. The patients either were maintained on the basal diet in the hospital or were allowed to continue their usual diet at home. In cases 1, 7, 11, 18, 25, 41, 50 and 69 the intramuscular injection of the amount of liver extract derived from 10 Gm. of liver daily or that derived from 100 Gm. of liver weekly completely relieved the symptoms referable to the tongue within from three to five days after the first injection. By the end of a week redness was gone and the reappearance of papillae in denuded areas of the tongue was observed. In the patients having diarrhea the frequency of the stools decreased, and within two weeks most of the stools were formed. The results of the observations in cases 11 and 18 are shown diagrammatically in chart 1. In two other patients (cases 52 and 63) the daily oral administration of liver extract derived from 300 Gm. of liver had a similar effect on the tongue. It thus appeared proper to regard improvement of the tongue in early sprue as a qualitative index of effective therapy comparable to the hematopoietic responses of the anemic patients.

70. Ashford, B. K., and Pons, J. A.: A Clinical Investigation of Thirteen Cases of Anemia of Pernicious Type in Porto Rico, *Porto Rico J. Pub. Health & Trop. Med.* **7**:167 (Dec.) 1931.

71. Oatway, W. H., Jr., and Middleton, W. S.: Correlation of Lingual Changes with Other Clinical Data, *Arch. Int. Med.* **49**:860 (May) 1932. Hutter, A. M.; Middleton, W. S., and Steenbock, Harry: Vitamin B Deficiency and the Atrophic Tongue, *J. A. M. A.* **101**:1305 (Oct. 21) 1933.

Castle and Strauss⁷² had observed that the lingual and gastrointestinal symptoms of pernicious anemia were relieved by such combinations of the extrinsic factor and the gastric juice of normal persons as resulted in hematopoietic effects. Various sources of the extrinsic factor, such as beef muscle,⁷³ eggs,^{64b} autolyzed yeast,⁶³ rice polishings,

CASE	SYMPTOMS PRESENT	DAYS					
		10	20	30	40	50	60
2	TONGUE						
	DIARRHEA						
	TREATMENT	L.E. Δ 20 GM. I.M. DAILY	NO THERAPY	VITAVOSE 45 GM. DAILY	MEAT AND MILK DIET DAILY	L.E. Δ 300 GM. DAILY	NO THERAPY
		DAYS (CONTINUED)					
		70	80	90	100		
2 (CONTINUED)	TONGUE						
	DIARRHEA						
	TREATMENT	300 GM. MEAT + 200 C.C. HCL DAILY	300 GM. MEAT + 150 CC GASTRIC JUICE DAILY	NO THERAPY	VENTRICULIN 30 GM. DAILY		
11		DAYS					
		10	20	30	40		
	TONGUE						
18	DIARRHEA						
	TREATMENT	NO THERAPY	L.E. Δ 100 GM. I.M.				
23		DAYS					
		10	20	30	40	50	60
	TONGUE						
26	DIARRHEA						
	TREATMENT	NO THERAPY	MEAT 300 GM. + HCL 200 CC DAILY				
41		DAYS					
		10	20	30	40	50	60
	TONGUE						
23	DIARRHEA						
	TREATMENT	NO THERAPY	VEGEX 16 GM. DAILY	MEAT 300 GM. + HCL 200 CC DAILY	MEAT 300 GM. + GASTRIC JUICE 200 CC DAILY	L.E. Δ 10 GM. DAILY	
26		DAYS					
		10	20	30	40	50	60
	TONGUE						
41	DIARRHEA						
	TREATMENT	NO THERAPY	MEAT 300 GM. + HCL 200 CC DAILY				
41		DAYS					
		10	20	30	40	50	60
	TONGUE						
41	DIARRHEA						
	TREATMENT	VEGEX 16 GM. DAILY		LE Δ 300 GM. p.o. DAILY			

Chart 1.—The effect of liver extract and of sources of the extrinsic factor administered alone or with gastric juice on the lingual and intestinal manifestations of sprue in the early stages or sprue with little anemia. Note that whereas liver extract always relieved the lingual symptoms, beef muscle was not effective in cases 2 and 23 until supplemented with normal human gastric juice. In this and the following charts the phrase L.E. Δ 100 Gm. means liver extract derived from 100 Gm. of liver.

72. Castle.^{62a} Strauss and Castle.⁶⁰

73. Castle.^{62a} Castle, Heath and Strauss.^{62b}

and wheat germ,^{64a} were shown to become hematopoietically active when administered with normal human gastric juice to suitable patients with pernicious anemia. Accordingly, certain of these substances in amounts known to be effective in the treatment of pernicious anemia only after contact with normal human gastric juice were administered to patients with incomplete sprue with and without the addition of normal human gastric juice. In chart 1 are shown diagrammatically the results of these observations. Patient 26, after a preliminary control period of six days, was given daily 300 Gm. of beef muscle and 200 cc. of tenth-normal hydrochloric acid. After about six days of this treatment the tongue began to improve and within two weeks clearly showed a reappearance of many of its papillae. In case 41, on the other hand, the daily administration of 16 Gm. of Vegex (a commercial preparation of autolyzed yeast) for fourteen days was without effect. Within two days after the subsequent daily oral administration of liver extract the glossitis began to improve, and within five days the tongue had no longer the signs of an inflammatory process. The explanation of these differences in the effectiveness in sprue of sources of extrinsic factor known to be potent in pernicious anemia only after contact with normal gastric juice was made clear by the following observations:

After a preliminary control period of five days, patient 23 received daily for ten days 16 Gm. of Vegex and during the succeeding period of ten days 300 Gm. of beef muscle and 200 cc. of tenth-normal hydrochloric acid. No effect on the severe glossitis of this patient was observed with either type of extrinsic factor. The dose of 200 cc. of hydrochloric acid was then replaced by 200 cc. of normal human gastric juice, while the administration of the beef muscle was continued as before. Three days later the lingual symptoms were less, and within ten days the tongue appeared entirely normal. Moreover, on the seventh day of the administration of the beef muscle and gastric juice a reticulocyte response of 4 per cent was obtained when the red blood cells numbered 1,400,000 per cubic millimeter. Liver extract derived from 20 Gm. of liver injected daily then caused a second reticulocyte peak of only 8.6 per cent. The tongue remained normal.

In case 2 a more extended series of observations was carried out, as shown in chart 1. It was demonstrated that the lingual symptoms and signs were not relieved in successive periods of ten days or more by the daily administration of 45 Gm. of Vitavose (an extract of wheat germ), of 300 Gm. of beef muscle and 1,500 cc. of milk, or of 300 Gm. of beef muscle and 200 cc. of tenth-normal hydrochloric acid, respectively. On the other hand, the substitution of 200 cc. of normal human gastric juice for the hydrochloric acid caused the tongue to improve after six days and to be entirely free from "inflammation" by the end of ten days.

TABLE 4.—Results of the Oral and Parenteral Administration of Liver

Days	Case 10				Case 15				Case 40				Case 41				Case 53				Case 54			
	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloocytes, per Cent	...	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloocytes, per Cent		Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloocytes, per Cent		Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloocytes, per Cent		Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloocytes, per Cent		Red Blood Cells, Millions	Hemoglobin, per Cent	Reticuloocytes, per Cent	
First Period: Daily Oral Administration of Liver Extract Derived from 300 Gm. of Liver and from 600 Gm. in Cases 78, 90 and 92																								
0.....	2.34	59	0.8		1.52	37	0.8		1.45	42	1.0		0.89	22	3.2		1.09	34	1.8		1.13	29	0.8	
2.....	2.52	64	2.6		1.66	41	0.4		1.73	41	1.6		0.81	23	3.2		0.95	30	2.1		0.39	24	0.6	
4.....	2.64	66	1.4		1.51	38	0.8		1.50	38	1.6		0.76	23	4.8		0.91	30	6.4		1.01	23	0.6	
6.....	2.59	63	5.4		1.67	44	5.8		1.73	40	2.2		0.79	24	6.4		0.94	31	17.2		0.89	22	1.6	
8.....	2.69	62	8.4		1.63	41	7.2		1.70	44	2.6		0.77	25	9.2		1.16	30	35.8		0.76	21	1.6	
10.....	2.62	68	5.4		2.00	44	4.8		1.76	46	2.2		0.91	27	8.0		1.24	33	30.2		0.80	22	8.4	
12.....					1.90	45	2.8										1.46	42	15.6					
14.....		1.52	44	10.6		
16.....	
18.....		1.89	56	3.6		
20.....		1.91	55	0.2		
22.....		1.90	45	2.0		
24.....	
26.....	
28.....		1.72	49	1.8			2.05	53	
5 weeks.....		2.14	50	1.0			3.45	76	1.2		
6 weeks.....		2.12	54	1.0		
7 weeks.....		2.16	54	0.8		
Second Period: Daily* Parenteral Administration of Liver Extract in Amounts Indicated																								
	L. E. Δ 10 i.m.†				L. E. Δ 10 i.m.				L. E. Δ 10 i.m.				L. E. Δ 10 i.m.				No Therapy				L. E. Δ 10 i.m.			
0.....	2.62	68	5.4		2.16	54	0.8		1.76	46	2.2		0.91	27	8.0			0.80	22	8.4	
2.....	2.74	69	2.2		1.97	48	1.6		1.52	45	3.0		0.97	25	5.8			0.86	22	16.0	
4.....	2.70	68	4.6		2.24	58	0.8		1.83	48	8.0		0.94	27	6.2			1.42	32	25.4	
6.....	2.66	67	2.0		2.38	63	0.6		2.32	51	15.0		0.99	28	23.0			1.83	28	15.0	
8.....	3.12	72	2.4		2.56	60	1.0			1.19	34	28.0			1.81	42	9.2	
10.....	2.95	68	2.2		2.30	62	2.0			1.35	34	15.2			1.73	46	5.0	
12.....	2.87	72	2.4		L. E. Δ 50 i.v.				2.95	58	1.8		1.59	38	4.0			2.00	46	4.0	
14.....	2.72	68	3.4		2.74	65	1.0			1.93	40	4.8			2.18	50	5.0	
16.....	2.72	72	1.4		2.63	58	1.0			2.37	42	3.6			2.27	55	3.6	
18.....	3.03	74	6.0		2.79	65	0.8			2.68	45	8.0			2.08	48	3.0	
20.....										2.80	55	2.8			2.17	55	2.2	
22.....		3.46	69	0.6		2.98	58	1.0			2.36	56	1.4	
24.....		2.41	57	1.6	
26.....		2.62	54	2.2	
28.....		3.05	59	1.4			2.75	55	2.2	
5 weeks.....		4.05	76		2.43	53	1.2	
																					Ferric Ammonium Citrate, 6 Gm.			
6 weeks.....		3.53	65	0.1			2.65	60	3.0	
7 weeks.....		3.98	75	1.2			2.50	61	0.8	
8 weeks.....	
9 weeks.....	
10 weeks.....	
11 weeks.....	
12 weeks.....	

* Exceptions should be noted in cases 90 and 92.

† Δ 10 indicates: derived from 10 Gm. of liver.

Extract in Amounts Effective in the Treatment of Pernicious Anemia

[illegible]

Second Period: Daily* Parenteral Administration of Liver Extract in Amounts Indicated

L. E. Δ 10 l.m.	L. E. Δ 10 l.m.	L. E. Δ 20 l.m.	L. E. Δ 10 l.m.	L. E. Δ 10 l.m.	L. E. Δ 100 l.v. Every 10 Days	L. E. Δ 100 l.v. Every 10 Days
1.78 46 3.0	1.93 55 1.6	1.51 37 8.6	0.83 26 14.0	1.11 29 10.2	2.24 57 3.6	1.00 23 2.6
1.70 48 2.8	2.35 59 1.0	1.47 46 5.2	0.92 29 8.0	1.34 34 11.2	2.32 60 2.4	1.04 21 2.4
1.63 49 4.4	2.49 62 1.0	1.54 43 2.4	1.03 30 6.0	1.40 36 8.2	2.53 63 2.2	1.36 29 29.8
1.35 46 5.0	2.78 63 0.8	1.65 45 4.2	1.06 31 8.0	1.60 40 3.4	3.10 69 6.0	1.69 32 20.4
1.60 43 3.0	2.63 60 1.8	1.60 44 5.4	1.26 35 4.2	1.69 41 2.8	2.80 67 2.6	1.83 34 10.2
L. E. Δ 300 p.o.	2.47 61 1.0	1.95 52 3.4	1.24 38 6.8	L. E. Δ 50 Every 4 Dn.	3.07 71 2.6
.... ..	2.83 68 0.8	2.27 52 3.6	1.52 42 3.0	1.40 42 5.6	2.95 68 1.0	2.29 40
....	1.51 42 4.8	3.39 75 1.0
.... ..	L. E. Δ 50 l.v.	1.43 42 2.8	1.85 46 1.6	3.69 73 1.2	3.63 45
2.53 58 2.8	2.50 69 1.2	1.67 44 4.4	3.39 78 1.4
.... ..	3.09 66 1.0	1.72 46 4.4	3.29 53
.... ..	2.54 63 1.0	2.92 62 3.6	1.72 46 4.4
.... ..	2.95 66 0.6	1.72 50 3.6
....	1.80 46 0.6	2.29 51 2.8	3.39 75
2.10 56 1.4	3.17 70	1.71 52 2.2	3.05 56
....	1.84 52 4.0	2.30 57 2.6
2.62 66	3.31 74 0.8	3.11 68	L. E. Δ 20 l.m.
....	2.50 62 2.8	3.41 64 0.6	3.91 69
2.50 63	3.76 79	2.68 68 1.8	3.69 63 0.4
3.03 64	3.80 79	2.94 68 2.0	3.78 62
3.21 60	2.99 65
....	3.27 67 0.8
....
....	3.40 68	4.63 73
....	3.74 71

Similarly, the oral administration of 30 Gm. of Ventriculin daily and the oral and intramuscular administration of liver extract each caused improvement of the tongue after the reappearance of "inflammation" during periods when therapy had been discontinued.

The interpretation of these results is clearly suggested by analogous observations in cases of pernicious anemia. The lingual and gastrointestinal symptoms of early sprue are thus apparently dependent on a deficiency mechanism, as already suggested but not delineated by Ashford,¹⁵ Elders¹⁸ and others.⁷⁴ Since liver extracts and combinations of the extrinsic and the intrinsic factor known to be capable of promoting the formation of blood in pernicious anemia influence favorably the glossitis of both diseases, the defect of nutrition producing the symptoms in the two diseases is apparently similar. In different patients with sprue, however, the disturbance was apparently brought about by different mechanisms resulting in the same final "liver extract" defect. Thus, in the patient in whom the glossitis was improved by the administration of the extrinsic factor alone (case 26) it is probable that the intrinsic factor was present in the gastric contents. On the other hand, in those patients (cases 2 and 23) in whom no improvement of the glossitis occurred until both the extrinsic and the intrinsic factor were administered it is probable that insufficient intrinsic factor was present to produce benefit without a supplement from a normal person. In its early manifestations sprue is thus clearly dependent on deficiencies closely related to, if not identical with, those already described in association with pernicious anemia.

Observations on Patients with Fully Developed Sprue and Anemia.—

In some patients with sprue oral therapy with liver extract or stomach preparations in amounts usually effective in the treatment of pernicious anemia has not produced significant improvement of the blood values.⁷⁵ This result has led to the assumption that the conditions producing the macrocytic blood picture in sprue are not always the same,⁷⁰ and some type of aplastic anemia has been hypothecated to explain the failure of therapy.⁷⁶ In table 4 are shown the hematopoietic results in 13 patients with advanced sprue and severe macrocytic anemia of the daily oral administration for a period of ten or more days of liver extract derived from 300 or 600 Gm. of liver, as indicated. Except in cases 40, 68, 90 and 92, the oral administration of this amount of liver extract provoked a significant increase in reticulocytes. This therapy was immediately followed in 9 cases by the daily intramuscular injection of the same

74. Maclean.⁷ Grant.⁸

75. Ashford, B. K.: An Evaluation of Liver Extract in the Treatment of the Anemias of Sprue, J. A. M. A. **91**:242 (July 28) 1928. Ashford and Pons.⁷⁰

76. Suárez.^{25b} Fairley, Mackie and Billimoria.⁴² Baumgartner.⁴³

extract derived from 10 Gm. of liver. In case 78 twice this dosage was employed. In cases 90 and 92 liver extract derived from 100 Gm. of liver was given intramuscularly at ten day intervals. In cases 40, 90 and 92, in which there had not been a reticulocyte response to orally administered liver extract, the intramuscular injection of this material resulted in a significant increase of reticulocytes. In case 68, in which likewise there was no response to oral therapy in the first period, although no reticulocyte response appeared from the daily intravenous administration of the liver extract derived from 50 Gm. of liver, the blood values rose steadily. In cases 44, 54 and 55 the first response to orally administered liver extract was not sufficiently great to prevent a second rise of the reticulocyte count in response to parenteral administration. In cases 10, 15, 78, 82 and 83 there was no second reticulocyte response to the parenteral administration of liver extract, but the blood values were progressively increased. Additional illustrations of the effectiveness of parenterally administered liver extracts will be found in tables 5, 6 and 11. In our experience the response of the lingual and gastro-intestinal symptoms in patients in the advanced stage of sprue was scarcely less striking than in patients in the early stages of the disease, especially when the material was given by parenteral injection. Since the anemia of all these patients was distinctly improved by means of a liver extract effective in pernicious anemia, administered if necessary by injection, the therapeutic failures noted by others with orally administered products do not necessarily indicate a different basis for the failure of production of blood in such cases of sprue. These results clearly suggest factors of deficiency in the advanced stage of the disease similar to those observed in sprue in the early stages and in addisonian pernicious anemia. Accordingly, a study was undertaken of the etiologic relationship of dietary deficiency, changes in gastric secretions and disturbances of intestinal absorption to fully developed sprue and anemia.

(a) Etiologic Significance of Deficiency of the Dietary (Extrinsic) Factor: The use of diets containing rare meat has attained some degree of success in the treatment of sprue and the associated anemia.⁷⁷ Ashford⁷⁵ and Baumgartner and Case⁷⁸ have described moderate reticulocyte responses with such a diet without liver. Since beef muscle is an excellent source of the extrinsic factor, the explanation of the hematopoietic effectiveness of these diets in the treatment of sprue is possibly afforded by the facts already discovered in connection with pernicious anemia⁷³ and by the observations on the tongue in cases of sprue already reported. If the analogies suggested are correct, in those

77. Ashford.²⁸ Manson-Bahr and Willoughby.³⁶ Elders.⁵⁴

78. Baumgartner, E. A., and Case, C. E.: Reticulocyte Response in a Case of Tropical Sprue on a Diet Not Including Liver, *Clifton M. Bull.* **16**:183, 1930.

TABLE 5.—Results of the Daily Addition to the Basal — of 300 Gm. of Beef Muscle and 1,500 Cc. of Milk, and of Subsequent Therapy with Orally and Parenterally Administered Liver Extract Effective in Pernicious Anemia

Days	Case 5				Case 17				Case 19				Case 22				Case 32				Case 35				Case 37				Case 42				Case 79			
	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent		Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent		Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent		Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent		Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent		Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent		Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent		Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent					
First Period: Daily Addition of 300 Gm. of Beef Muscle and 1,500 Cc. of Milk to Basal Diet																																				
0.....	1.21	44	1.4		2.56	75	1.2		1.55	36	0.6	1.98	56	0.8	1.23	31	0.8	2.14	50	0.8	1.62	42	0.8	2.18	63	0.8	2.18	63	0.8	1.46	40	0.4				
2.....	1.78	45	2.8		2.46	72	1.0		1.23	32	1.0	2.18	53	0.8	1.27	28	0.8	1.75	46	0.6	1.58	44	0.4	2.46	65	1.0	2.46	65	1.0	1.38	38	1.0				
4.....	1.56	44	2.2		2.66	81	2.4		1.21	30	2.6	2.47	53	0.8	1.30	29	1.2	1.92	46	1.4	1.53	40	0.4	2.53	65	0.8	2.53	65	0.8	1.48	37	1.0				
6.....	1.51	48	1.6		2.68	79	3.6		1.22	32	3.0	2.35	53	0.8	1.10	31	0.4	2.14	50	1.0	1.75	47	0.8	2.31	61	0.8	2.31	61	0.8	1.51	39	2.8				
8.....	1.43	44	3.4		2.70	79	4.4		1.19	30	3.6	2.17	54	0.6	1.01	29	0.8	1.87	46	1.0	1.88	43	1.4	2.34	66	0.8	2.34	66	0.8	1.47	41	5.0				
10.....	1.61	54	8.6		2.96	77	4.6		1.25	32	2.2	2.22	54	0.8	1.25	28	0.6	...	44	1.8	1.85	43	1.8	2.20	64	1.0	2.20	64	1.0	1.62	41	3.2				
12.....	1.67	43	6.4			1.24	32	2.0	2.31	55	1.0	1.00	31	1.0	1.78	46	1.2	1.70	42	2.2	2.56	61	4.2	2.56	61	4.2				
14.....	1.51	53	7.0		3.20	78	2.6		1.07	26	1.6	2.24	58	0.8	1.10	27	1.0	1.77	44	1.6	1.92	42	2.0	2.86	62	6.2	2.86	62	6.2				
16.....	1.58	54	2.6			1.14	26	2.0	2.35	53	2.4	1.55	44	1.8	2.05	50	2.8	2.64	63	1.8	2.64	63	1.8				
18.....	1.36	49	3.8		2.88	78	3.4		1.32	27	2.0	2.45	56	2.8	1.85	48	3.0	2.20	51	2.0	2.67	64	1.2	2.67	64	1.2				
20.....	1.83	56	1.8		3.37	82	1.8		1.11	29	1.8	2.36	57	2.6	1.85	50	2.0	2.85	64	1.0	2.85	64	1.0				
22.....	1.91	51	1.8			1.14	25	1.6	2.40	58	1.6	1.65	46	2.0			
24.....	2.31	57	1.4		2.81	73	1.0		2.70	65	1.4	1.82	46	2.0			
26.....	2.88	73	2.0		2.88	73	2.0		2.45	65	1.6	1.64	46	4.6			
28.....	2.90	70	1.4		2.90	70	1.4		2.54	64	0.6	2.30	52	2.4			
5 weeks.....	2.76	64	0.8	2.49	47	2.4			
6 weeks.....		
Second Period: Daily Oral Administration of Liver Extract Derived from 300 Gm. of Liver																																				
0.....	2.02	57	1.4		2.90	70	1.4		1.14	25	1.6	1.04	31	1.8	2.49	47	2.4	1.59	42	1.6	2.85	64	1.0	2.85	64	1.0	1.62	41	3.2				
2.....	2.19	61	1.6		2.81	69	1.6		0.96	25	2.0	1.15	31	1.4	2.73	47	1.6	1.56	38	2.0	2.69	69	1.0	2.69	69	1.0	1.70	43	2.8				
4.....	2.18	64	0.6		3.10	64	3.2		1.06	27	3.4	0.89	33	1.0	2.64	50	1.8	1.78	45	2.4	2.70	63	0.8	2.70	63	0.8	1.64	37	1.6				
6.....	2.11	61	0.8		3.20	65	1.0		1.01	26	4.2	1.23	31	2.0	2.58	49	2.0	2.09	45	2.0	2.85	60	0.8	2.85	60	0.8	1.33	36	1.2				
8.....	1.84	60	0.8		2.96	68	1.4		1.19	29	2.4	1.18	34	2.8	2.51	50	1.6	1.87	47	1.6	2.76	58	5.6	2.76	58	5.6	1.25	35	0.4				
10.....	1.76	56	2.4		3.39	69	1.2		1.28	26	1.6	1.51	37	7.4	2.65	51	1.0	1.74	47	0.8	2.77	58	7.8	2.77	58	7.8				
12.....	1.36	38	4.6			
14.....	1.48	40	4.0			
3 weeks.....		
Thlrd Period: Daily Parenteral Administration of Liver Extract Derived from 10 Gm. of Liver																																				
0.....	1.76	56	2.4		3.39	69	1.2		1.28	26	1.6	1.48	40	4.0	2.72	50	2.2	1.74	47	0.8	2.44	57	3.6	2.44	57	3.6	1.25	35	0.4				
2.....	1.87	53	1.6		3.27	65	1.4		0.98	22	1.6	1.25	38	1.6	2.56	48	2.2	1.77	46	0.8	2.77	58	3.2	2.77	58	3.2	1.70	39	3.8				
4.....	1.55	55	1.8		2.99	61	2.6		1.02	26	4.0	1.47	40	1.0	3.02	49	1.0	1.80	49	0.8	2.79	54	2.8	2.79	54	2.8	1.62	40	4.3				
6.....	1.97	58	2.2		3.57	65	1.8		1.08	25	15.8	1.59	45	1.4	2.99	49	1.6	1.74	48	1.4	2.57	56	5.0	2.57	56	5.0	1.53	40	9.2				
8.....		3.19	53	1.6		1.50	30	9.2	1.36	40	3.6	3.04	50	1.0	1.97	49	2.8	2.94	59	7.0	2.94	59	7.0	1.51	42	8.4				
10.....	2.81	61	4.0		3.46	62	2.0		1.65	42	1.2	3.21	51	1.6	1.74	48	5.9	3.20	57	4.6	3.20	57	4.6	1.55	46	4.8				
12.....	3.00	63	4.2			1.45	26	6.0	1.59	44	1.0	1.90	50	5.2	2.97	55	3.2	2.97	55	3.2	1.51	44	3.4				
14.....	2.60	64	7.2			1.92	29	5.0	1.60	44	1.2	3.12	49	1.4	2.37	54	4.8	3.28	58	2.6	3.28	58	2.6	1.58	44	2.6				
16.....	2.70	69	2.4			1.37	23	6.4		
18.....	2.76	72	2.4			1.50	26	4.8	1.96	45	2.0		
20.....	2.96	69	4.0			
22.....	
24.....	
26.....	
28.....	

patients with sprue and macrocytic anemia in whom sufficient intrinsic factor is present in the gastric juice (and in whom intestinal absorption is adequate) the administration of beef muscle alone should provoke a reticulocyte response. These conditions were apparently satisfied in 5 of our 9 patients given, in addition to the basal diet, 300 Gm. of meat and 1,500 cc. of milk daily. In cases 5, 17, 19, 42 and 79 there was attained a significant increase in the reticulocyte count which became maximal by the end of fourteen days of such therapy (table 5). In cases 22, 35 and 37 a delayed reticulocyte response of doubtful significance occurred, but a gradual increase in red blood cells took place. In case 32 no evidence of increased hematopoietic activity appeared. In 4 of these 9 patients (cases 17, 19, 32 and 42) the subsequent daily oral administration of liver extract derived from 300 Gm. of liver produced a second rise in the reticulocyte count (table 5). Subsequent daily parenteral administration of liver extract derived from 10 Gm. of liver produced a reticulocyte response in cases 5, 19, 37, 42 and 79.

Another active source of the extrinsic factor in pernicious anemia is autolyzed yeast.⁶⁴ Observations were accordingly made under controlled conditions on the effects of two preparations of autolyzed yeast on 9 patients with sprue and severe anemia. Dried brewers' yeast was mixed with a small amount of water and placed in the incubator for periods of from ten to fourteen days or until the material had turned brown and had a characteristic odor. This preparation of autolyzed yeast was given daily to 6 patients in amounts indicated in terms of the original weight of dried yeast (table 6). Four of these patients (cases 2, 9, 31 and 68) showed a reticulocyte response; the 2 remaining patients (cases 15 and 40) did not. In case 15 there was subsequently a response to orally administered liver extract with a significant rise in reticulocytes; there was none in case 40. In case 40 in response to the subsequent parenteral administration of liver extract a significant increase in reticulocytes appeared. A commercial preparation of autolyzed yeast, Vegex, was administered in daily doses of 12 or 16 Gm., as indicated in table 6, during the first periods of observation on another patient (case 86). A questionable reticulocyte response appeared. In 2 other patients (cases 49 and 72) liver extract derived from 300 Gm. of liver was given daily during the first period of observation and resulted in a significant reticulocyte response. In each patient in the second period larger reticulocyte responses were obtained from the daily administration of 12 Gm. of Vegex. It is thus clear that in cases 49 and 72 the effect of 12 Gm. of Vegex was greater than the effect of liver extract derived from 300 Gm. of liver.

In summarizing the results obtained from the administration to 18 patients of sources of the extrinsic factor consisting of either beef

TABLE 6.—Results of the Oral Administration of Preparations of Autolyzed Yeast and of Oral and Parenteral Administration of Liver Extract

Days	Autolyzed Yeast, 60 Gm. Case 2				Autolyzed Yeast, 120 Gm. Case 9				Autolyzed Yeast, 180 Gm. Case 15				Autolyzed Yeast, 120 Gm. Case 31				Autolyzed Yeast, 180 Gm. Case 40				Autolyzed Yeast, 120 Gm. Case 68				Veget, 16 Gm. Case 86				L. E. Δ 300 Case 49				L. E. Δ 300 Case 72			
	Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Millions			
0	1.56	32	3.4	1.98	53	1.2	2.06	50	1.0	1.28	49	4.0	1.38	45	2.0	1.32	47	3.6	1.50	50	3.4	0.57	18	1.0	0.87	22	1.2	0.87	22	1.2	0.87	22	1.2			
2	1.85	34	1.8	2.00	51	0.8	1.80	53	1.2	1.60	45	3.0	1.23	45	1.6	1.44	47	2.4	2.00	52	1.6	0.62	16	1.4	0.92	20	1.0	0.92	20	1.0	0.92	20	1.0			
4	1.73	34	2.8	2.48	53	2.6	1.73	47	0.8	1.42	48	6.6	1.45	45	1.0	1.83	53	1.2	2.15	55	1.8	0.85	18	5.0	0.98	20	1.8	0.98	20	1.8	0.98	20	1.8			
6	1.45	35	7.8	2.12	56	4.0	1.73	45	0.8	1.32	42	4.0	1.45	46	1.0	1.55	50	1.2	1.76	51	2.4	0.58	18	5.8	0.78	18	7.4	0.78	18	7.4	0.78	18	7.4			
8	1.69	38	8.4	2.25	55	6.8	1.69	40	0.8	1.69	40	0.8	1.25	42	0.8	1.68	55	4.6	1.91	57	2.6	0.60	18	6.8	0.98	25	16.0	0.98	25	16.0	0.98	25	16.0			
10	1.72	35	12.8	2.42	60	8.2	1.79	45	0.8	1.26	41	2.6	1.45	42	1.0	1.70	50	3.0	2.22	55	3.6	0.76	17	3.0	1.25	31	16.4	1.25	31	16.4	1.25	31	16.4			
12	1.81	38	4.6	2.39	56	5.4	1.42	41	2.2	1.42	41	2.2	1.45	42	1.0	1.70	50	3.0	2.15	52	3.8	0.76	17	3.0	1.25	31	16.4	1.25	31	16.4	1.25	31	16.4			
14	2.01	38	3.6	2.36	57	2.4	1.42	41	2.2	1.42	41	2.2	1.45	42	1.0	1.70	50	3.0	2.15	52	3.8	0.76	17	3.0	1.25	31	16.4	1.25	31	16.4	1.25	31	16.4			
16	1.77	37	3.8	2.15	54	1.8	1.42	41	2.2	1.42	41	2.2	1.45	42	1.0	1.70	50	3.0	2.15	52	3.8	0.76	17	3.0	1.25	31	16.4	1.25	31	16.4	1.25	31	16.4			
18	1.98	37	3.8	2.37	62	2.0	1.42	41	2.2	1.42	41	2.2	1.45	42	1.0	1.70	50	3.0	2.15	52	3.8	0.76	17	3.0	1.25	31	16.4	1.25	31	16.4	1.25	31	16.4			
20	2.10	38	3.4	2.59	66	2.4	1.42	41	2.2	1.42	41	2.2	1.45	42	1.0	1.70	50	3.0	2.15	52	3.8	0.76	17	3.0	1.25	31	16.4	1.25	31	16.4	1.25	31	16.4			
22	2.71	74	1.8	2.71	74	1.8	1.42	41	2.2	1.42	41	2.2	1.45	42	1.0	1.70	50	3.0	2.15	52	3.8	0.76	17	3.0	1.25	31	16.4	1.25	31	16.4	1.25	31	16.4			
24	2.51	67	3.0	2.51	67	3.0	1.42	41	2.2	1.42	41	2.2	1.45	42	1.0	1.70	50	3.0	2.15	52	3.8	0.76	17	3.0	1.25	31	16.4	1.25	31	16.4	1.25	31	16.4			
26	2.50	59	1.2	2.50	59	1.2	1.42	41	2.2	1.42	41	2.2	1.45	42	1.0	1.70	50	3.0	2.15	52	3.8	0.76	17	3.0	1.25	31	16.4	1.25	31	16.4	1.25	31	16.4			
28	2.23	56	4.4	2.23	56	4.4	1.42	41	2.2	1.42	41	2.2	1.45	42	1.0	1.70	50	3.0	2.15	52	3.8	0.76	17	3.0	1.25	31	16.4	1.25	31	16.4	1.25	31	16.4			
First Period: Daily Oral Administration of Various Substances as Indicated																																				
Second Period: Daily Oral Administration of Various Substances as Indicated																																				
Third Period: Daily Parenteral Administration of Liver Extract Derived from 10 Gm. of Liver																																				
0	2.10	38	3.4	2.23	56	4.4	1.52	37	0.8	1.42	41	2.2	1.45	42	1.0	1.88	58	1.4	1.99	55	2.0	0.76	17	3.0	1.25	31	10.4	1.25	31	10.4	1.25	31	10.4			
2	2.00	39	3.8	2.12	51	4.2	1.66	41	0.4	1.42	42	2.6	1.73	41	1.6	2.26	65	0.8	2.18	57	2.2	0.70	21	4.8	1.37	38	10.8	1.37	38	10.8	1.37	38	10.8			
4	2.19	39	4.6	1.98	54	1.8	1.51	38	0.8	1.24	37	3.4	1.50	38	1.6	1.87	53	1.2	2.34	55	1.2	0.80	19	3.0	1.78	38	13.4	1.78	38	13.4	1.78	38	13.4			
6	1.92	46	5.4	2.01	51	1.2	1.07	44	5.8	1.38	39	3.2	1.73	40	2.2	1.94	56	1.6	1.83	52	1.0	0.70	18	5.6	2.01	40	17.4	2.01	40	17.4	2.01	40	17.4			
8	1.79	41	3.0	1.66	46	2.0	1.63	41	7.2	1.10	34	5.7	1.70	44	1.8	2.10	59	1.8	2.02	52	1.4	0.74	20	9.8	2.35	45	8.6	2.35	45	8.6	2.35	45	8.6			
10	2.49	40	3.6	2.04	50	2.2	2.00	44	4.8	1.25	40	5.7	1.76	46	2.2	1.93	55	1.6	1.88	50	1.2	0.81	22	14.6	1.90	53	5.8	1.90	53	5.8	1.90	53	5.8			
12	2.21	53	1.0	2.21	53	1.0	1.59	45	2.8	1.32	43	3.8	1.76	46	2.2	1.93	55	1.6	2.11	58	2.2	1.00	27	12.8	1.46	51	5.8	1.46	51	5.8	1.46	51	5.8			
14	2.21	53	1.0	2.21	53	1.0	1.59	45	2.8	1.32	43	3.8	1.76	46	2.2	1.93	55	1.6	2.11	58	2.2	1.00	27	12.8	1.46	51	5.8	1.46	51	5.8	1.46	51	5.8			
16	2.21	53	1.0	2.21	53	1.0	1.59	45	2.8	1.32	43	3.8	1.76	46	2.2	1.93	55	1.6	2.11	58	2.2	1.00	27	12.8	1.46	51	5.8	1.46	51	5.8	1.46	51	5.8			
18	2.21	53	1.0	2.21	53	1.0	1.59	45	2.8	1.32	43	3.8	1.76	46	2.2	1.93	55	1.6	2.11	58	2.2	1.00	27	12.8	1.46	51	5.8	1.46	51	5.8	1.46	51	5.8			
20	2.21	53	1.0	2.21	53	1.0	1.59	45	2.8	1.32	43	3.8	1.76	46	2.2	1.93	55	1.6	2.11	58	2.2	1.00	27	12.8	1.46	51	5.8	1.46	51	5.8	1.46	51	5.8			
22	2.21	53	1.0	2.21	53	1.0	1.59	45	2.8	1.32	43	3.8	1.76	46	2.2	1.93	55	1.6	2.11	58	2.2	1.00	27	12.8	1.46	51	5.8	1.46	51	5.8	1.46	51	5.8			
24	2.21	53	1.0	2.21	53	1.0	1.59	45	2.8	1.32	43	3.8	1.76	46	2.2	1.93	55	1.6	2.11	58	2.2	1.00	27	12.8	1.46	51	5.8	1.46	51	5.8	1.46	51	5.8			
26	2.21	53	1.0	2.21	53	1.0	1.59	45	2.8	1.32	43	3.8	1.76	46	2.2	1.93	55	1.6	2.11	58	2.2	1.00	27	12.8	1.46	51	5.8	1.46	51	5.8	1.46	51	5.8			
28	2.21	53	1.0	2.21	53	1.0	1.59	45	2.8	1.32	43	3.8	1.76	46	2.2	1.93	55	1.6	2.11	58	2.2	1.00	27	12.8	1.46	51	5.8	1.46	51	5.8	1.46	51	5.8			
(table 4)																																				
0	2.49	40	3.6	2.21	53	1.0	2.16	54	0.8	1.21	46	3.4	1.76	46	2.2	1.93	55	1.6	1.76	41	2.0	1.18	25	5.2	1.46	51	5.8	1.46	51	5.8	1.46	51	5.8			
2	2.34	40	3.2	1.67	48	1.4	1.97	48	1.6	1.28	41	2.6	1.52	45	3.0	2.35	59	1.0	1.60	40	1.8	1.09	30	5.4	2.36	54	3.8	2.36	54	3.8	2.36	54	3.8			
4	2.11	38	1.4	2.27	48	1.2	2.24	48	0.8	1.28	35	2.2	1.83	48	3.0	2.49	63	1.0	1.59	38	1.0	1.15	29	4.6	2.51	55	3.2	2.51	55	3.2	2.51	55	3.2			
6	2.59	44	3.8	2.27	50	2.6	2.38	63	0.6	1.37	44	1.6	2.32	51	15.0	2.78	63	0.8	1.56	38	3.0	1.02	32	5.6	2.59	54	1.8	2.59	54	1.8	2.59	54	1.8			
8	2.63	41	1.6	2.23	47	1.6	2.56	60	1.0	1.37	41	1.6	2.32	51	15.0	2.78	63	0.8	1.56	38	3.0	1.02	32	5.6	2.59	54	1.8	2.59	54	1.8	2.59	54	1.8			
10	2.59	38	1.6	2.38	53	2.0	2.30	62	2.0	1.32	44	6.8	2.35	58	1.8	2.83	68	0.8	1.71	52	12.6	1.21	34	7.2	2.55	55	1.0	2.55	55	1.0	2.55	55	1.0			
12	2.40	45	1.4	2.74	65	1.0	2.63	58	1.0	1.83	51	6.6	2.35	58	1.8	2.83	68	0.8	1.90	45	9.6	1.34	36	5.4	2.84	57	1.0	2.84	57	1.0	2.84	57	1.0			
14	2.23	40	3.2	2.23	40	3.2	2.63	58	1.0	1.83	51	6.6	2.35	58	1.8	2.83	68	0.8	1.90	45	9.6	1.34	36	5.4	2.84	57	1.0	2.84	57	1.0	2.84	57	1.0			
16	2.23	40	3.2	2.23	40	3.2	2.63	58	1.0	1.83	51	6.6	2.35	58	1.8	2.83	68	0.8	1.90	45	9.6	1.34	36	5.4	2.84	57	1.0	2.84	57	1.0	2.84	57	1.0			
18	2.33	48	3.6	2.79	65	0.8	2.79	65	0.8	2.12	53	3.6	2.55	56	2.6	3.09	66	1.0	2.54	53	2.8	1.47	41	7.0	3.17	60	1.0	3.17	60	1.0	3.17	60	1.0			
20	2.33	48	3.6	2.79	65	0.8	2.79	65	0.8	2.12	53	3.6	2.55	56	2.6	3.09	66	1.0	2.54	53	2.8	1.47	41	7.0	3.17	60	1.0	3.17	60	1.0	3.17	60	1.0			
22	2.33	48	3.6	2.79	65	0.8	2.79	65	0.8	2.12	53	3.6	2.55	56	2.6	3.09	66	1.0	2.54	53	2.8	1.47	41	7.0	3.17	60	1.0	3.17	60	1.0	3.17	60	1.0			
24	2.33	48	3.6	2.79	65	0.8	2.79	65	0.8	2.12	53	3.6	2.55	56	2.6	3.09																				

muscle or preparations of autolyzed yeast, case 40 must be excluded. In this case there was no reticulocyte response to any material, including liver extract, when orally administered. Since the subsequent reticulocyte response to parenterally administered liver extract was definite, some degree of intestinal impermeability probably rendered the patient unsuitable for the trial of orally administered material. In 11 of the remaining 17 patients there was a significant reticulocyte response which attained a peak on or before the fourteenth day of therapy. Three patients (cases 22, 35 and 37) showed a gradual increase in the blood values without a definite reticulocyte response at the expected time. In case 86 no trial of orally administered liver extract followed the doubtful response to Vegex. In case 22 no subsequent determination of the response of the patient to orally administered liver extract was made. In the 2 remaining cases (15 and 32) there was no reticulocyte response to sources of the extrinsic factor, but there was a subsequent response to orally administered liver extract in a dosage not as effective in cases 49 and 72 as the daily oral administration of 12 Gm. of Vegex. In cases 15 and 32 it was therefore impossible to detect the presence of the intrinsic factor by the administration of material containing the extrinsic factor. In 3 patients (cases 22, 35 and 37) a minimal amount of intrinsic factor was probably present but distinctly less than in the 11 patients who responded to the administration of the extrinsic factor with a rise in reticulocytes. Thus, the ability to react favorably to sources of the extrinsic factor, whether judged by the reticulocyte response or by the improvement of the tongue, is a variable condition in different patients with sprue. It is therefore logical to examine the possibility that many cases of sprue are produced by deficiency of the diet. Herein the situation in sprue apparently differs from that in pernicious anemia in that a defect of the intrinsic factor of the stomach is almost invariably found in patients with classic addisonian pernicious anemia in relapse.⁷⁹ On the contrary, in treated patients with pernicious anemia Barnett⁷⁹ has apparently observed the presence of the intrinsic factor, which under these circumstances has also been observed to reappear when previously absent.^{62b} Incidentally, because of the fact that sources of the extrinsic factor without added gastric juice were found to be hematopoietically effective in certain patients with sprue, grave doubt is thrown on the inferences of Morris and his co-workers⁸⁰ who alleged that the defect in pernicious anemia does not involve a

79. Barnett, C. W.: The Significance of the Gastric Secretions in Pernicious Anemia, *Am. J. M. Sc.* **182**:170 (Aug.) 1931.

80. Morris, R. S.; Schiff, Leon; Burger, George, and Sherman, J. E.: A Specific Hematopoietic Hormone in Normal Gastric Juice, *J. A. M. A.* **98**:1080 (March 26) 1932.

reaction with an extrinsic factor but depends solely on a defect of the gastric secretion.

Accordingly, an investigation was made of the individual diets of 63 of the 92 patients selected entirely at random. Particular attention was paid to the character of the diet for years before the onset of the disease. The method of taking the dietary histories included questioning the patient as to his particular likes and dislikes in food and as to whether his diet differed in any way from that of other members of his family. He was asked to describe an average daily menu. In addition, he was questioned as to the number of times per day, week or month that he ate specific foods common in the Puerto Rican diet. Although the taking of a dietary history is admittedly a difficult procedure in which the quality of the patient's answers may be as important as his quantitative statements in indicating the amount and type of food taken, the monotony of the fare of the Puerto Rican peasants aided the investigation by limiting the possibilities.

In table 7 an attempt has been made to present in a roughly quantitative manner the individual consumption of those articles of diet which might be considered to be important from the standpoint of sources of complete proteins, the extrinsic factor, vitamins and mineral elements, including iron. Thus, the data do not represent the chief sources of energy of the Puerto Rican diet but merely indicate those foodstuffs considered to be of special nutritional significance. The figures represent as nearly as could be determined the average number of times, without reference to quantity consumed, that the particular type of food mentioned was eaten during a period of one month. It is to be clearly understood that the figures are estimates and are necessarily of only approximate accuracy. From an inspection of the data, however, it is at once apparent that the consumption of meat, milk, eggs, whole grain cereals and butter was extremely low in many of these cases. Thus, meat, excluding chicken, was never eaten by 14 and was eaten only once a week or less frequently by 30 of the 63 patients. Eleven patients ate no eggs, and 18 consumed one egg or less a week. Thirty-five patients used no whole grain cereals, and 43 indulged in this type of food once a week or less frequently. Nineteen patients ate no butter. Milk was utilized mainly in small amounts in coffee unless indicated in the table by an asterisk. Fresh fish was rarely used, and the values in table 7 refer almost entirely to salt codfish. Green vegetables, such as lettuce, chard, string beans, chayote, okra and other Puerto Rican products, were largely employed in garnishing the main staples, rice and beans. Twenty patients were able to state the average daily cost of their food. The most expensive diet cost \$1; the least expensive, 10 cents. The average daily expenditure for food was 33 cents, which

TABLE 7.—*Number of Times per Month, Without Reference to Quantity, That the Foods Listed Were Consumed by Patients with Sprue*

Case	Meat	Milk	Eggs	Fish	Whole Cereals	Green Vegetables	Fruit	Butter
1.....	12	0	0	0	0	30	30	4
2.....	1	8	8	20	0	4	6	0
3.....	30	30*	0	6	6	30	30	30
4.....	4	90*	30	1	1	4	30	4
5.....	0	60	12	1	0	12	30	0
6.....	4	90*	60	6	0	30	60	0
7.....	30	30	30	12	4	60	60	30
9.....	30	30	30	16	12	16	8	30
10.....	3	30	30	4	30	8	20	20
11.....	4	30	1	4	0	0	30	0
12.....	4	30	8	8	30	4	20	8
16.....	30	30	30	12	0	0	30	4
17.....	0	30	30	0	8	0	20	0
18.....	0	30	30	6	6	6	8	30
19.....	6	30	8	6	4	8	20	0
21.....	12	90	60	8	30	10	30	30
22.....	0	0	0	8	0	6	2	20
23.....	16	30	20	8	4	8	30	30
26.....	8	30	30	4	15	20	30	0
27.....	30	30	30	12	0	12	20	30
28.....	4	30	30	30	0	0	30	0
29.....	6	30	30	20	0	6	15	0
30.....	8	6	6	6	12	15	30	0
31.....	2	30	0	2	0	4	15	0
32.....	10	30	6	6	30	8	10	20
34.....	0	30	30	2	0	16	4	4
35.....	4	20	10	10	0	0	30	0
36.....	0	90*	30	0	0	0	20	0
37.....	4	30	90	0	20	0	30	..
39.....	4	10	3	30	8	30	30	0
42.....	8	8	12	8	0	0	30	12
44.....	30	30	30	0	0	8	45	0
48.....	4	30	30	0	0	0	30	30
49.....	20	30	30	30	30	30	45	30
50.....	20	30	60	0	30	30	30	12
51.....	40	30	30	4	2	30	60	12
52.....	25	30	16	0	0	40	40	..
53.....	6	60	12	8	30	30	2	30
54.....	5	60	0	1	0	2	60	30
55.....	0	20	0	0	0	0	10	..
57.....	0	30	30	0	0	30	60	30
59.....	8	30	30	6	0	10	15	..
61.....	6	30	1	0	0	8	40	0
62.....	16	40	60	0	0	12	30	8
63.....	4	0	0	30	0	15	10	..
64.....	0	60*	0	0	0	0	30	..
65.....	0	30	4	0	0	24	20	..
66.....	2	30*	30	0	3	10	30	..
67.....	30	60*	60	0	0	3	40	..
68.....	30	60*	15	4	30	20	40	0
69.....	2	60*	30	0	0	30	30	0
70.....	12	60	30	30	30	60	6	30
73.....	30	90*	240	4	4	10	15	..
74.....	20	0	30	4	12	12	40	..
75.....	0	30	0	0	0	30	30	8
77.....	0	90*	4	4	6	6	30	0
79.....	8	30	12	8	0	12	40	30
80.....	12	3	1	2	0	4	15	4
82.....	12	90*	10	12	0	0	10	8
84.....	16	30	0	12	12	4	60	30
85.....	12	30	16	6	30	12	16	2
86.....	0	30	4	4	4	0	16	..
89.....	0	90*	0	2	0	2	20	6

* This includes milk other than that used in coffee.

must have greatly exceeded the abilities of several patients whose daily bread was largely the offering of charitable neighbors.

Ashford,⁸¹ whose long residence in Puerto Rico and painstaking study has given him an intimate knowledge of the dietary habits of the sufferer from sprue, has vividly described the situation. He has said in part:

The Northern visitor to endemic centers in the tropics will usually find that, much against his will, he must consume an abnormally large quantity of greasy food. . . . He finds the native vegetables uncultivated, fibrous, and mawkish to his palate, and he seeks his calories, not in the tough, freshly-killed local beef, but in starches and sugars, the only familiar articles of diet at hand. We should here note the very well-known lack of nutritious fresh foods in certain tropical countries which, like Porto Rico, have to subsist on gold crops such as tobacco, coffee and sugar in order to support their enormous native populations. . . . Such peoples live chiefly on grain foods imported from the North; the laborer on highly polished rice, beans, and codfish, with a few rough tubers; the upper stratum on canned foods and a large variety of carbohydrates, pieced out with an inferior quality of milk and such vegetables as they can get from the meager local markets.

It is thus probable that the usual type of diet is such as to favor a diminished consumption of some of the known sources of the extrinsic factor, such as meat, eggs and whole grain cereals. Our recent parallel study²⁹ of the dietary histories of a group of patients with hookworm infection and anemia in Puerto Rico further attests the prevalence of defective nutrition in persons with anemia.

In this connection, it is interesting that in certain extreme instances of the general malnutrition of a group or community diarrheal conditions resembling sprue have been observed to become epidemic. In 1877 an epidemic of this type appeared during a famine in India. The postmortem appearance of the victims was carefully studied by Cunningham,⁸² who reported atrophic changes in the mucosa of the small intestine and less marked alterations in the colon which are certainly suggestive of sprue. McCarrison¹⁹ presented evidence of the importance of malnutrition in the etiology of "famine" and "jail" dysentery. Guarini⁸³ has reported 40 cases of gastro-enteritis followed by chronic enlargement of the abdomen among prisoners in the World War who were badly fed. Ashford⁸⁴ noted the appearance of sprue, pellagra and beriberi in association with deficient diet in Puerto Rico.

81. Ashford, B. K.: Sprue, *Ann. Clin. Med.* **4**:13 (July) 1925.

82. Cunningham, D. D.: Fourteenth Annual Report of the Sanitary Commissioners with the Government of India, Calcutta, 1877.

83. Guarini, Carlo: Ricerche radiologiche sul così detto "grosso ventre di guerra" nei soldati reduci dalla prigionia, *Riforma med.* **36**:30 (Jan. 10) 1920.

84. Ashford, B. K.: Dietetic Deficiencies Predisposing to Sprue, Pellagra and Beri-Beri in Porto Rico. *Bull. Porto Rico M. A.* **15**:249, 1921.

(b) Etiologic Significance of Defect of the Gastric (Intrinsic) Factor: On the other hand, a direct dietary defect of the extrinsic factor cannot be the entire cause of the condition of all patients with sprue because not all patients are improved by the addition of the extrinsic factor alone. The problem in this respect resembles that in addisonian pernicious anemia, in which the extrinsic factor in the usual amounts is rarely hematopoietically effective without the addition of the intrinsic factor. The observations on the tongues of patients with sprue in the early stages demonstrated that in certain instances the extrinsic factor was not effective until the intrinsic factor was added. In the advanced stage hematopoietic responses have demonstrated the same fact. It has been inferred from this that in certain patients with sprue a defect of the intrinsic factor exists, as in patients with pernicious anemia. In order to establish this point fully the content of intrinsic factor of the gastric juice of 3 patients with sprue was determined by observations of its hematopoietic effect, after contact with the extrinsic factor, on patients with addisonian pernicious anemia. These observations were carried out on patients at the Thorndike Memorial Laboratory of the Boston City Hospital with the collaboration of Dr. Maurice B. Strauss.

Patient 90 was an American planter from Puerto Rico with sprue of ten years' standing. Patient 91 was an American physician who had paid a yearly visit to Puerto Rico for many years but had had sprue for only a year. Patient 92 was an American minister from China who had suffered from sprue for seven years. In all 3 cases the use of diets for sprue containing beef muscle had been unsuccessful in controlling symptoms. The anemia in cases 90 and 92 was definitely macrocytic. In case 91 there was little anemia but severe diarrhea. The gastric contents of each of the patients contained free hydrochloric acid, and a test for pepsin made in cases 91 and 92 was positive (table 9). Assays for the intrinsic factor were made by methods already described,^{62b} involving the daily administration of from 50 to 75 cc. of gastric contents from each patient with sprue, together with 200 Gm. of beef muscle, to suitable patients with pernicious anemia for a period of ten days. During subsequent periods of ten days normal human gastric juice in equal amounts was substituted for the gastric juice of the patients with sprue without other change in the conduct of the observation.

In table 8 are shown the detailed results of these observations. A reticulocyte response occurred in a suitable patient with pernicious anemia (test case C) as a result of the daily administration of 50 cc. of the gastric contents of patient 91 together with 200 Gm. of beef muscle. The subsequent administration of an equal quantity of normal human gastric juice under identical conditions did not produce

TABLE '8.—Results of Tests on Patients with Pernicious Anemia of the Hematopoietic Effect of an Extract of the Liver of a Patient with a Fatal Case of Sprue, and of the Gastric Juice in Cases 90, 91 and 92 Administered with Beef Muscle

[illegible]

a second rise of the reticulocyte count. On the contrary, no reticulocyte response was produced by the daily administration of 75 cc. of the gastric juice of patients 90 and 92, respectively, with 200 Gm. of beef muscle to each of 2 patients with pernicious anemia (test cases B and D). A reticulocyte response, however, promptly appeared in each patient with pernicious anemia (cases B and D) when equal quantities of normal human gastric juice were administered with beef muscle in immediately subsequent periods. A month after the first assay of the gastric juice of patient 92 for the intrinsic factor the test was repeated with 50 cc. of gastric contents and 200 Gm. of beef muscle daily, again with negative results.

From these direct observations on the effect of the gastric juice of patients with sprue on patients with pernicious anemia it is clear that the intrinsic factor was present in the gastric juice of patient 91 but not in that of patients 90 and 92, at least not in detectable amounts. As a control on the method of testing for the intrinsic factor, utilized in other patients with sprue in Puerto Rico, patient 92 was given 200 Gm. of beef muscle daily for a period of ten days, without producing a rise in the number of reticulocytes. The hematopoietic effect in pernicious anemia of the administration of 200 Gm. of beef muscle and 150 cc. of normal human gastric juice is about equal to that of 150 Gm. of prepared liver.^{62b} Since the patient immediately thereafter responded to the daily administration of 150 Gm. of prepared liver with a rise in the reticulocyte count, it is clear that sufficient intrinsic factor was not present to produce a hematopoietic effect with the beef muscle. This result, then, agrees entirely with the negative result of the test involving a patient with pernicious anemia. These observations, taken with those made in Puerto Rico, are considered to constitute highly suggestive evidence that patients with sprue in both the early and the late stages may lack detectable amounts of the intrinsic factor usually absent in patients with addisonian pernicious anemia in relapse.

Thus, in sprue, as has been pointed out before for pernicious anemia,^{62b} the chemical analysis of the gastric contents is found to be an inadequate index of the presence of the intrinsic factor. The presence of hydrochloric acid in the gastric contents in cases of sprue may be associated either with the presence (case 91) or with the absence (cases 90 and 92) of the intrinsic factor. With these reservations the results of chemical analysis of the gastric contents of 65 of our patients with sprue are shown in table 9. The results are also indicated for those patients in whom assays of the presence or absence of detectable amounts of the intrinsic factor were made by one of the methods

TABLE 9.—*Results of Analysis of Gastric Contents for Free Hydrochloric Acid, Pepsin and Intrinsic Factor*

Case	Titration of Free Hydrochloric Acid in Cc. N/10 Sodium Hydroxide			Peptic Activity after Egg White, Mm. per 24 Hr.	Intrinsic Factor
	After 7% Alcohol		After Histamine, 20 Min.		
	20 Min.	40 Min.			
1.....	0	0	0	0	..
2.....	0	0	38	8	+
3.....	66	70	84	5	..
4.....	90	96	97	16	..
5.....	45	49	67	14	+
9.....	0	0	18	8	+
10.....	43	30	48	6	..
12.....	0	0	8	8	..
15.....	83	78	93	9	0
16.....	0	0	33	9	..
17.....	5	8	54	11	+
19.....	0	0	0	..	+
21.....	0	0	3	8	..
22.....	0	0	0	0	±
23.....	40	13	83	7	..
26.....	8	0	38	8	..
28.....	38	50	70	10	..
29.....	0	0	13	19	..
30.....	0	0	0	0	..
31.....	0	0	0	9	+
32.....	5	11	0	9	0
34.....	25	45	62	11	..
35.....	0	0	0	6	±
36.....	0	9	0	5	..
37.....	0	0	0	4	±
38.....	13	31	63	7	..
39.....	0	0	0	2	..
40.....	0	0	80	10	..
42.....	41	20	78	10	+
44.....	0	0	0	0	..
45.....	0	0	0	5	..
47.....	10	18	53	0	..
49.....	0	0	0	0	+
50.....	15	0	43	8	..
51.....	0	0	0	0	..
52.....	14	5	15	12	..
53.....	0	0	0	0	..
54.....	0	0	0	0	..
55.....	0	0	3	7	..
56.....	20	55	83	6	..
57.....	0	0	0	2	..
59.....	0	0	23	6	..
60.....	0	0	0	6	..
61.....	30	25	60	8	..
64.....	8	29	35	10	..
65.....	0	0	4	8	..
68.....	28	25	39	6	+
70.....	4	0	10	9	..
72.....	0	0	0	5	..
74.....	25	15	24	6	..
75.....	0	0	0	6	..
76.....	0	0	32	10	..
79.....	5	40	72	9	+
80.....	15	1	23	7	..
81.....	0	0	0	4	..
82.....	24	45	78	15	..
83.....	17	35	71
84.....	0	0	30	8	..
85.....	33	24	0	8	..
86.....	5	5	40	13	±
87.....	0	0	0
88.....	50	0	57	24	..
90.....	32	37	40	..	0
91.....	7	12	17	11	+
92.....	27	53	70	10	0

described earlier. It is believed, however, on the basis of the work of Mettier and Minot,⁸⁵ that gastric anacidity may have a bearing on the absorption of iron from the upper intestinal tract and so may be of importance in predisposing the patient with sprue to the development of hypochromic anemia in certain instances.

Ashford²⁸ found achlorhydria in 39 per cent of 41 patients with sprue; Baumgartner and Smith,^{37b} in one third of 15 patients, and Fairley and his associates,⁸⁶ in about 27 per cent of 26 patients. These values, obtained with broth or with Ewald test meals, correspond fairly well with our findings in 65 patients with sprue who were examined once, usually soon after coming under observation. In 33 (51 per cent) of our patients free hydrochloric acid was secreted in response to the ingestion of 50 cc. of 7 per cent alcohol; in 12 (18 per cent) acid was secreted only after the subcutaneous injection of 0.5 mg. of histamine phosphate, and in 20 (31 per cent) there was no secretion of hydrochloric acid. Estimations of pepsin were made by the use of Mett's tubes in the most acid sample of the gastric contents, which was, if necessary, brought to p_H 1.8 with hydrochloric acid. The egg albumin of the Mett tubes was coagulated at 85 C. In 7 of 18 patients in whom there was no secretion of free hydrochloric acid no pepsin was secreted. In only 1 of 8 patients in whom there was no secretion of pepsin was hydrochloric acid secreted. With 1 exception in all patients in whom there was secretion of free hydrochloric acid pepsin was also secreted.

(c) Etiologic Significance of Defects of Absorption: The variations in the responses of patients with pernicious anemia to orally administered liver extract are seemingly greater than those to parenterally administered material. Since in our experience the active principle of liver extract is not appreciably affected by autoclaving or by digestion with pepsin and hydrochloric acid or, according to Reimann, Sinek and Fritsch,⁸⁷ by digestion with trypsin or erepsin, it is probably not destroyed in the intestinal tract. On the other hand, the intrinsic factor especially might well be more susceptible to destruction^{62b} by enzymes. The influence of difficulty in the absorption of hematopoietic substances

85. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastroduodenal Contents in Certain Cases of Anemia, *Am. J. M. Sc.* **181**:25 (Jan.) 1931.

86. Fairley, N. H.; Mackie, F. P.; Chitre, G. D.; Gokhale, S. K.; Gore, S. N.; Malandkar, M. A., and Sacasa, F. J.: A Progress Report on Researches in Sprue (1924-1925), *Indian J. M. Research* **14**:105 (July) 1926.

87. Reimann, F.; Sinek, F., and Fritsch, F.: Untersuchungen zur Leberwirkung bei der Anaemia perniciosa, *Ztschr. f. klin. Med.* **41**:126, 1933.

in pernicious anemia has already been suggested.⁸⁸ It is, however, impossible to assert this as a proved fact because it is not known what are exactly comparable doses of liver extract both on oral and on parenteral administration. Even with parenterally administered liver extract the variation in response, due possibly to differences in its internal utilization in certain patients, may be as great as evidently exists with orally administered material. In this communication the effectiveness of the daily oral administration of liver extract derived from 300 Gm. of liver has usually been compared with the daily parenteral administration of an aqueous solution of this material derived from 10 Gm. of liver. From the observations of Minot and his associates^{33a, b} it is clear that maximal reticulocyte responses are not usually obtained with this dosage of liver extract administered orally. On the other hand, prior to these observations on sprue it was discovered by Strauss, Taylor and Castle⁸⁹ that the daily parenteral administration of this material derived from 10 Gm. of liver will usually produce a reticulocyte response comparable to those obtained from the daily oral administration of liver extract derived from 600 Gm. of liver. Therefore, in these observations on sprue a trifling reticulocyte response to the daily oral administration of material derived from 300 Gm. of liver, even when followed by a large response to the daily parenteral administration of the same product derived from 10 Gm. of liver in a subsequent period, is not necessarily evidence of intestinal impermeability. Moreover, experience with pernicious anemia has shown that a certain proportion of the patients who are resistant to oral therapy are also resistant to a certain extent to parenteral therapy. At present, therefore, the existence of intestinal impermeability must remain only a logical possibility.

Observations on various types of anemia, however, favor such a supposition. Keefer and his associates⁹⁰ have shown that among patients with intestinal tuberculosis the degree of hypochromic anemia is greater in those who have diarrhea. The development of pernicious

88. (a) Schilling, V.: Gänsslens injizierbares Leberextrakt, *Klin. Wchnschr.* **10**:301 (Feb. 14) 1931. (b) Isaacs, Raphael; Sturgis, C. C.; Goldhamer, S. M., and Bethell, F. H.: The Use of Liver Extract Intravenously in the Treatment of Pernicious Anemia, *J. A. M. A.* **100**:629 (March 4) 1933. (c) Castle, Heath and Strauss.^{62b}

89. Strauss, M. B.; Taylor, F. H. L., and Castle, W. B.: Intramuscular Use of Liver Extract: Maximal Responses of Reticulocytes from Daily Intramuscular Injection of Extract Derived from Ten Grams of Liver: Preliminary Communication, *J. A. M. A.* **97**:313 (Aug. 1) 1931.

90. Keefer, C. S.; Huang, K. K., and Yang, C. S.: The Importance of Under-nutrition in the Production of Anemia Associated with Chronic Dysentery and Tuberculosis of the Intestine, *Nat. M. J. China* **15**:743, 1929.

anemia in patients with intestinal obstruction⁹¹ or anastomosis of the small intestine⁹² has been reported. In sprue the changes in the microscopic appearance of the intestinal wall are suggestive of dysfunction, and in this condition as well as in celiac disease⁹³ and chronic diarrhea of various types⁹⁴ there is evidence of a disturbance of the absorption of fat and of inorganic elements. Thus, the fatty stools and occasional tetany of sprue are not based on any definite evidence of parathyroid or pancreatic deficiency⁹⁵ but correspond to the findings in diarrheal conditions, such as celiac disease, in which split fats and calcium are not well absorbed or are lost in the stools in excessive amounts.⁹³ In a disease in which diarrhea and evidence of gastro-intestinal disturbance exist to the extent encountered in sprue and in which fats and calcium are clearly not always well absorbed, it is not unnatural to believe that difficulty in the absorption of hematopoietic substances may occur. If not due to changes in the intestinal wall this effect could result from the diarrhea.

A common history in our patients was that formerly a diet for the treatment of sprue had relieved the symptoms or improvement had taken place and had been maintained with a given amount of liver extract orally administered. By the time they were observed by us, diets for sprue and oral therapy with liver extract were no longer as effective as they had been. The statements of some of these patients were confirmed by observations under controlled conditions. In no instance, however, was relief not forthcoming with sufficient amounts of parenterally administered liver extract. Although it is impossible to state whether an original dosage of parenterally administered material would not have become proportionately inadequate, this fact is suggestive of

91. Faber, Knud: Perniciöse Anämie bei Dünndarmstricturen, Berl. klin. Wchnschr. **34**:643 (July 26) 1897. Meulengracht, E.: Pernicious Anemia in Intestinal Stricture, with Report of One Liver-Treated Case, Acta med. Scandinav. **72**:231, 1929.

92. Little, W. D.; Zervas, L. G., and Trusler, H. M.: Chronic Obstruction of the Small Bowel: Result of Two Entero-Enterostomies and Apparently the Cause of Pernicious Anemia, J. A. M. A. **93**:1290 (Oct. 26) 1929. Castle, Heath and Strauss.^{62b}

93. Bennett, T. I.; Hunter, Donald, and Vaughan, J. M.: Idiopathic Steatorrhea (Gee's Disease): A Nutritional Disturbance Associated with Tetany, Osteomalacia and Anaemia, Quart. J. Med. **1**:603, 1932.

94. Linder, G. C., and Harris, C. F.: Calcium and Phosphorus Metabolism in Chronic Diarrhoea with Tetany, Quart. J. Med. **23**:195 (Jan.) 1930.

95. Ashford, B. K., and Hernández, L. G.: Blood-Serum Calcium in Sprue and Other Pathologic States in the Tropics, Am. J. M. Sc. **171**:575 (April) 1926. Sokhey, S. S., and Malandkar, M. A.: Pancreatic Function in Sprue, Indian J. M. Research **15**:921 (April) 1928.

a progressive difficulty with the absorption of hematopoietic substances. The following history is illustrative:

When first under observation patient 92 responded to the daily oral administration of 150 Gm. of liver. Subsequently the blood values approached normal as a result of the daily ingestion of liver extract derived from 300 Gm. of liver. A year later, however, the patient reentered the hospital because despite the daily ingestion of liver extract derived from 600 Gm. of liver the red blood cells had declined to a level of about 1,000,000 per cubic millimeter. Under observation in the hospital the daily oral administration for ten days of the same amount of liver extract produced a very slight reticulocyte response (table 4). A single intravenous injection of liver extract derived from 100 Gm. of liver, however, at once produced a large

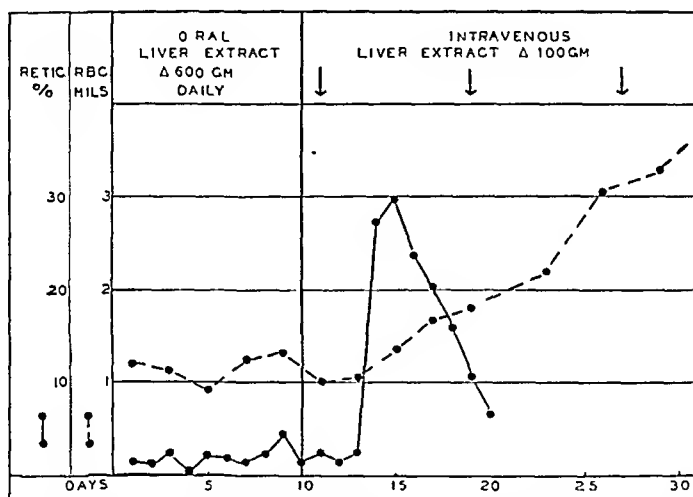


Chart 2.—A comparison of the hematopoietic effects of liver extract administered orally and then parenterally in case 92. The large daily oral dose of liver extract derived from 600 Gm. of liver was without significant hematopoietic effect, in contrast to the striking effect of a single intravenous injection of the same extract derived from 100 Gm. of liver. This probably indicates an abnormal degree of intestinal impermeability to hematopoietic substances.

reticulocyte response, and the blood values rose rapidly. These results are graphically portrayed in chart 2. Since that time, for three years, this patient has remained in excellent health with regular intramuscular injections of liver extract.

It would simplify our concept of the mechanism of the disease if the progressive changes in the effectiveness of oral therapy could be attributed with certainty to an increase in intestinal impermeability. For the reasons stated earlier, this cannot be done. Nevertheless, an arbitrary standard has been applied to the observations on these patients in an attempt to indicate in which cases, in our opinion, the suspi-

cion of intestinal impermeability was most justified. If the reticulocyte response to the daily oral administration of liver extract derived from 300 Gm. of liver or more was less than one third of that expected in similar patients with pernicious anemia,^{33a, b} and if the reticulocyte response to the subsequent daily parenteral injection of the same liver extract derived from 10 Gm. of liver was greater than two thirds of this expected value, the patient was considered arbitrarily to have some degree of intestinal impermeability. On the basis of these standards, patients 40, 44, 54, 86 and 92 are considered to fulfil the requirements. This conclusion should, however, be accepted with all the reservations set forth in the foregoing discussion of the difficulties of the problem.

(d) Deficiency of Hematopoietic Substance in the Liver in a Fatal Case of Sprue with Severe Macrocytic Anemia: Richter, Ivy and Kim⁹⁶ have found that extracts of the livers of patients who die of pernicious anemia in relapse do not contain hematopoietic substances, at least in the amounts present in the livers of normal persons. If the mechanisms of deficiency in sprue outlined previously resemble those in addisonian pernicious anemia, the livers of patients with sprue and severe macrocytic anemia should be similarly deficient.

A test of this fact was made on the occasion of the death of a patient with sprue and severe anemia (case 81). The patient's condition was so grave on admission to the hospital that he died twenty-four hours later despite an injection of liver extract derived from 100 Gm. of liver and a transfusion of 300 cc. of blood. At autopsy the observations were typical of uncomplicated sprue.

An extract of the patient's liver suitable for parenteral injection was therefore made. Seven hundred and sixty grams of liver pulp was placed in 2,500 cc. of cold water and vigorously stirred for half an hour. Concentrated hydrochloric acid was added to bring the mixture to p_H 5. It was then boiled for five minutes and placed in the icebox for twelve hours. The original 2,000 cc. of filtrate and the second filtrate derived from a resuspension of the residue in 2,000 cc. of water at p_H 5 were combined and evaporated to dryness at 60 C. The precipitate was taken up in 1,000 cc. of 70 per cent alcohol, a small undissolved residue being washed again with 200 cc. of 70 per cent alcohol. The 1,200 cc. of combined filtrates was evaporated to 320 cc. at 60 C. To this filtrate was added sufficient absolute alcohol to reach a concentration of 95 per cent by volume. Six hundred cubic centimeters of ether was then added, and sedimentation was allowed to take place in the icebox. The precipitate was later dried at 60 C. and was found to amount to 28.21 Gm. of a whitish-yellow powder. The liver of a

96. Richter, O.; Ivy, A. C., and Kim, M. S.: Action of Human "Pernicious Anemia Liver Extract," *Proc. Soc. Exper. Biol. & Med.* **29**:1093 (June) 1932.

patient without anemia who died of acute cardiac dilatation was identically treated with the same original amount of liver pulp and reagents.

The extracts made of the livers of patient 81 and of the control patient were dissolved in water, neutralized and sterilized by Berkefeld filtration. The volume of each solution was such that 20 cc. of each contained the material derived from 100 Gm. of liver pulp. Into a suitable patient with pernicious anemia (test case *A*) was injected daily for eight days 5 cc. of the extract, which was the amount derived from 25 Gm. of the liver of patient 81. No significant reticulocyte response occurred (table 8). During an immediately subsequent period of twelve days 5 cc. of the extract derived from 25 Gm. of the liver of the control patient was injected daily. This produced a peak of the reticulocyte count on the eighth day of 9.4 per cent. In a subsequent period of ten days (not shown in table 8) the amount of liver extract derived from 25 Gm. of animal liver was injected daily, without a further reticulocyte response. Thus, the liver of the patient who died of sprue and severe macrocytic anemia did not contain detectable amounts of hematopoietic substance, in contrast to the liver of the control subject without anemia. This result further substantiates the evidence for a resemblance between the fundamental deficiency in sprue with macrocytic anemia and that in Addisonian pernicious anemia.

(*e*) Etiologic Significance of Accessory Deficiency of Iron to the Anemia: From the observations of several workers⁹⁷ it is evident that the anemia of sprue may be either macrocytic or hypochromic. The resemblance of the macrocytic type of anemia of sprue to the blood picture of pernicious anemia has been pointed out by others⁹⁸ and confirmed by the present observations. Even in pernicious anemia, however, the blood picture is not so constant as was commonly supposed. Now that the diagnosis and the physiologic responses of pernicious anemia can be studied by means of liver extract it is clear that classic uniformity of the blood picture is not always present. Indeed, the anemia typical of the syndrome described by Thomas Addison merges by a series of rarer intermediate forms with that of idiopathic hypochromic anemia with gastric anacidity.⁹⁹ It is known that pernicious anemia in responding to liver extracts may assume the characteristics of hypochromic anemia

97. Ashford.²⁸ Fairley, Mackie and Billimoria.⁴² Baumgartner.⁴³

98. Baumgartner and Smith.^{37b} Reed and Wyckoff.³⁸ Musser.⁴⁰ Fairley, Mackie and Billimoria.⁴²

99. (*a*) Wilkinson, J. F., and Brockbank, William: The Importance of Familial Achlorhydria in the Aetiology of Pernicious Anaemia, *Quart. J. Med.* **24**:219 (Jan.) 1931. (*b*) Heath, C. W.: The Interrelation of Pernicious Anemia and Idiopathic Hypochromic Anemia: The Study of a Family in Which Both Conditions Occurred Singly and Combined, *Am. J. M. Sc.* **185**:365 (March) 1933. Faber and Gram.⁵³

and require iron therapy for complete remission.¹⁰⁰ Heath^{99b} has recently studied the members of a family in which appeared types of anemia initially resembling pernicious anemia or hypochromic anemia, respectively. He was able to convert one type into the other by the appropriate use of either liver extract or iron over considerable periods of time. The physiologic concept here encounters no such difficulties as are imposed by the limitations of a rigid nosologic classification. It merely supposes that by a suitable proportion of deficiency of "liver extract," of "iron," and possibly of other substances the morphology of anemias ranging from macrocytic through normocytic to microcytic and hypochromic may be produced. Its supporters can demonstrate that the physiologic response of these differing types of anemia are dependent on the differing nature of the deficiency involved.¹⁰¹

The findings in the blood of 40 patients with pernicious anemia mostly in the first relapse have been contrasted with those for the 92 patients with sprue in table 2. Probably owing to the selection for macrocytic anemia exercised in choosing the patients with sprue, only 6 patients had a color index of less than unity, and of those only 2 had a mean corpuscular volume of less than the normal for the method. Otherwise, as mentioned previously, the blood picture of the patients with sprue was typical of pernicious anemia. The obviously defective diets of many of these patients with sprue resembled somewhat those of a parallel series of patients with hookworm disease and hypochromic anemia studied in Puerto Rico.²⁹ The 54 patients with hypochromic anemia showed an incidence of gastric anacidity (24 per cent) only slightly less than that observed in the 65 patients with sprue (31 per cent). Of 47 patients with hookworm disease who were adequately studied, 8 gave a history or showed evidence of lingual changes and 24 had had moderately severe diarrhea. Thus, the distinction between sprue with hypochromic anemia and hookworm disease with lingual and intestinal symptoms was necessarily arbitrary in some instances. In the same community hypochromic anemia without hookworm infection, which responded readily to therapy with iron, was common. In patients with Addisonian pernicious anemia, whose diet is relatively good, perhaps the highest incidence of a uniformly macrocytic anemia is found. On the other hand, as the factor of dietary deficiency or of intestinal disturbance becomes more pronounced the possibility of a defect of iron metabolism becomes greater and the

100. Beebe, R. T., and Lewis, G. E.: The Maintenance Dose of Potent Material in Pernicious Anemia, *Am. J. M. Sc.* **181**:796 (June) 1931.

101. Watkins, C. H.: Classification of Idiopathic Secondary Anemia, *Proc. Staff Meet., Mayo Clin.* **4**:19, 1929. Davies, D. T.: Studies on Achlorhydria and Anaemia, *Quart. J. Med.* **24**:447 (July) 1931. Minot and Heath.^{32d}

TABLE 10.—Results of the Administration of Ferric Ammonium

	Autolyzed Yeast, 60 Gm.				Autolyzed Yeast, 120 Gm.				Beef Muscle, 300 Gm.; Milk, 1,500 Cc.				Beef Muscle, 300 Gm.; Milk, 1,500 Cc.				L. E. Δ 100 l.m. Every 10 Days			
	Case 2				Case 9				Case 17				Case 19				Case 30			
Days	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent
First Period: Administration of Various Substances as Indicated																				
0	1.56	32	1.02	3.4	1.98	53	1.33	1.2	2.56	75	1.47	1.2	1.55	36	1.16	0.6	1.35	41	1.32	2.8
2	1.85	33	0.89	1.8	2.00	51	1.27	0.8	2.46	72	1.46	1.0	1.23	32	1.30	1.0	1.35	35	1.30	0.8
4	1.73	34	0.98	2.8	2.48	58	1.16	2.6	2.66	81	1.52	2.4	1.21	30	1.24	2.6	1.43	45	1.57	9.8
6	1.45	35	1.20	7.8	2.12	56	1.32	4.0	2.68	79	1.47	3.6	1.22	32	1.31	3.0	1.53	48	1.57	22.2
8	1.69	38	1.12	8.4	2.25	56	1.22	6.8	2.70	79	1.46	4.4	1.19	30	1.26	3.6	1.93	49	1.27	12.2
10	1.72	35	1.01	12.8	2.42	60	1.24	8.2	2.96	77	1.30	4.6	1.25	32	1.28	2.2	1.74	41	1.18	5.4
12	1.81	38	1.04	4.6	2.39	56	1.17	5.4	3.20	78	1.21	2.6	1.24	32	1.29	2.0	2.15	47	1.09	5.8
14	2.01	38	0.94	3.6	2.36	57	1.21	2.4	1.07	26	1.21	1.6	2.18	50	1.15	4.8
16	1.77	36	1.01	4.8	2.15	54	1.26	1.8	2.88	78	1.35	3.4	1.14	26	1.14	2.0
18	1.98	37	0.93	3.8	2.37	62	1.32	2.0	3.37	82	1.21	1.8	1.32	27	1.02	2.0
20	2.10	38	0.90	3.4	2.59	66	1.27	2.4	1.11	29	1.31	1.8	2.18	49	1.12	6.0
22	L. E. Δ 300 p.o. Daily				2.71	74	1.37	1.8	2.81	73	1.30	1.0	1.14	25	1.10	1.6
24	2.19	39	0.89	4.6	2.51	67	1.33	3.0	2.88	73	1.27	2.0	L. E. Δ 300 p.o. Daily			
26	1.92	46	1.19	5.4	2.50	59	1.18	1.2	2.90	70	1.21	1.4	1.06	27	1.27	3.4	2.77	59	1.07	1.2
28	1.79	41	1.14	3.0	2.23	56	1.26	4.4	L. E. Δ 300 p.o. Daily				1.01	26	1.29	4.2
30	2.49	40	0.80	3.6	L. E. Δ 300 p.o. Daily				3.10	64	1.03	3.2	1.19	29	1.22	2.4
32	L. E. Δ 10 i.m. Daily				1.98	54	1.36	1.8	3.20	65	1.02	1.0	1.28	26	1.02	1.6	2.81	56	1.00	1.2
Weeks													L. E. Δ 10 i.m. Daily							
5	2.59	44	0.84	3.8	1.66	46	1.39	2.0	3.39	69	1.02	1.2	1.02	26	1.27	4.0	2.51	55	1.16	1.0
	L. E. Δ 300 p.o. Daily				L. E. Δ 10 i.m. Daily				L. E. Δ 10 i.m. Daily											
6	2.51	37	0.73	2.4	1.67	48	1.44	1.4	3.46	62	0.90	2.0	1.08	25	1.16	15.8	3.42	57	0.83	1.0
7	2.94	40	0.68	...	2.38	53	1.11	2.0					1.50	26	0.87	4.8	3.39	60	0.89	0.8
					L. E. Δ 50 i.m. Daily															
8	2.33	48	1.03	3.6	3.11	50	0.80	...
9	2.79	44	0.78				
Second Period: Administration of Ferric Ammonium Citrate as Indicated																				
	Ferric Ammonium Citrate, 6 Gm. Daily				L. E. Δ 50 i.m. Daily Ferric Ammonium Citrate, 6 Gm. Daily				L. E. Δ 10 i.m. Daily Ferric Ammonium Citrate, 6 Gm. Daily				Ferric Ammonium Citrate, 6 Gm. Daily				Ferric Ammonium Citrate, 6 Gm. Daily			
0	2.79	44	0.78	...	2.33	48	1.03	3.6	3.46	62	0.90	2.0	1.50	26	0.87	4.8	3.11	50	0.80	...
2	2.35	44	0.94	3.8	3.28	66	1.01	3.8	1.58	23	0.73	6.4
4	3.65	54	0.74	...	2.42	43	0.89	5.2	3.00	64	1.07	5.6	1.97	26	0.66	10.4
6	2.15	47	1.09	5.0	3.36	64	0.95	5.4	1.96	30	0.77	7.2
8	3.87	49	0.63	...	2.35	48	1.02	7.6	Ferric Ammonium Citrate, 6 Gm. Daily				2.18	33	0.76	5.6	3.60	56	0.78	...
10	2.58	48	0.93	6.0					1.83	30	0.82	2.0
12	3.96	53	0.67	...	2.31	49	1.06	3.0	L. E. Δ 50 i.m. Daily			
14	4.90	79	0.81	3.0	2.06	39	0.95	1.0
Weeks																				
3	3.87	67	0.87	...	3.37	69	1.02	1.6	1.92	36	0.94	1.8	3.90	65	0.83	...
4	4.11	64	0.78	...	3.25	61	0.94	2.2	2.36	35	0.74	3.6	3.56	64	0.90	...
5	3.54	67	0.95	...	4.75	81	0.85	1.4	2.55	38	0.75	...	L. E. Δ 300 p.o. Daily Ferric Ammonium Citrate, 6 Gm. Daily			
6	L. E. Δ 300 p.o. Daily Ferric Ammonium Citrate, 6 Gm. Daily				4.32	67	0.79	1.6
7	4.40	68	0.77	1.0	3.17	70	1.10	4.08	66	0.81	0.6
8	4.09	64	0.78	...
9	4.53	75	0.83	0.6	3.52	71	1.01	3.74	64	0.86	...
10												

Citrate Subsequent to Therapy with Liver Extract

L. E. Δ 10 i.m. Daily Case 34				L. E. Δ 100 i.m. Once Case 43				L. E. Δ 300 p.o. Daily Case 52				L. E. Δ 300 p.o. Daily Case 61				L. E. Δ 10 i.m. Daily Case 79			
Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Color Index	Reticulocytes, per Cent
First Period: Administration of Various Substances as Indicated																			
2.78	55	0.99	2.4	0.55	17	1.55	0.6	2.76	56	1.01	6.8	0.91	26	1.43	5.8	1.25	35	1.40	0.4
2.70	58	1.04	3.0	0.65	18	1.38	0.73	25	1.71	8.0	1.70	39	1.15	3.8
2.98	58	0.97	2.8	0.66	18	1.36	10.0	0.83	25	1.51	10.0	1.62	40	1.23	5.2
3.12	64	0.87	2.0	0.56	23	2.05	17.0	0.70	25	1.58	8.4	1.56	40	1.28	9.2
3.38	57	0.84	3.0	0.80	25	1.56	14.8	3.14	49	0.78	1.6	0.90	27	1.50	9.2	1.51	42	1.39	8.4
3.18	55	0.87	2.8	0.79	25	1.58	9.2	1.06	33	1.56	15.0	1.55	46	1.48	4.8
2.88	55	0.97	1.6	0.79	26	1.65	5.4	0.87	35	2.01	12.0	1.51	44	1.46	2.6
3.23	58	0.90	2.4	1.06	27	1.28	4.8	3.51	47	0.66	0.6	0.86	30	1.74	7.2	1.58	44	1.39	3.4
L. E. Δ 50 i.m. Daily				0.72	26	1.81	9.0	L. E. Δ 10 i.m. Daily				1.69	47	1.39	3.8
2.85	55	0.96	3.0	1.23	30	1.22	7.0	0.98	34	1.73	4.8	1.71	47	1.37	5.2
3.00	52	0.86	2.0	1.50	34	1.13	8.0	1.10	34	1.55	5.0	1.91	52	1.36	2.2
2.92	48	0.82	2.2	1.65	33	1.00	6.0	2.95	45	0.76	...	1.17	37	1.58	6.6	2.14	51	1.19	2.2
....	1.45	35	1.21	6.6	1.15	39	1.70	7.2	1.97	49	1.24	3.0
....	1.65	35	1.06	3.8	1.26	39	1.55	3.8	1.89	51	1.35	3.4
....	1.71	35	1.02	4.6	3.65	48	0.65	0.4	1.81	56	1.21	2.4
....	2.13	34	0.80	2.0	1.57	42	1.34	3.0	2.23	55	1.23	2.0
....	2.60	39	0.75	2.6	2.36	60	1.27	2.4
....	2.24	37	0.83	2.0	3.20	47	0.73	0.2	2.25	45	1.00	...	2.45	57	1.16	5.4
....	L. E. Δ 300 p.o. Daily				3.56	47	0.66	1.2	2.64	50	0.95	...	2.74	64	1.17	1.2
....	2.80	40	0.71	1.2	3.21	45	0.70	...	2.41	49	1.02	...	2.77	65	1.17	1.2
....	2.97	41	0.69	0.8	3.34	67	1.00	...
....	3.15	69	1.10	...
Second Period: Administration of Ferrie Ammonium Citrate as Indicated																			
L. E. Δ 50 i.m. Daily Ferrie Ammonium Citrate, 6 Gm. Daily				Ferrie Ammonium Citrate, 6 Gm. Daily				Ferrie Ammonium Citrate, 6 Gm. Daily				Ferrie Ammonium Citrate, 6 Gm. Daily				Ferrie Ammonium Citrate, 6 Gm. Daily			
2.92	48	0.82	2.2	2.97	41	0.68	0.8	3.21	45	0.70	...	2.41	49	1.02	...	3.15	69	1.10	...
2.90	51	0.88	2.6	3.26	43	0.66	0.6	3.33	72	1.08	1.6
2.89	53	0.92	3.4	3.23	44	0.68	1.4	2.43	48	0.99	...	3.30	68	1.03	1.0
2.84	55	0.97	6.8	3.78	39	0.52	1.6	3.60	75	1.04	1.0
3.49	59	0.85	6.0	3.14	43	0.68	1.2	3.80	50	0.66	1.4	2.60	53	1.02	...	3.39	73	1.08	0.6
2.93	57	0.97	6.4	3.24	46	0.71	5.8
3.81	64	0.84	5.0	3.36	50	0.74	3.0	2.78	54	0.97
....	4.47	53	0.59	1.0
Ferrie Ammonium Citrate, 6 Gm. Daily				4.40	56	0.64	...	2.70	50	0.93	...	4.01	76	0.95	...
4.00	71	0.89	1.4	2.99	52	0.87
4.41	71	0.80	0.6	Add L. E. Δ 20 i.m. Daily				2.46	53	1.08
4.53	75	0.83
4.81	80	0.83	3.04	58	0.95	...	3.82	80	1.05	...
4.85	83	0.86	3.29	65	0.99
....	3.62	63	0.87
....	3.43	67	0.98
....	3.70	72	0.97

finding of hypochromic anemia becomes more common, as in pellagra,^{52a} celiac disease,⁹³ chronic dysentery⁹⁰ or sprue.²⁸

The frequent appearance of hypochromic anemia in sprue clearly suggests the possible influence of some degree of "iron" deficiency on the anemia in combination with the effects of the "liver extract" deficiency leading to lingual and gastro-intestinal symptoms and to macrocytic anemia. In a few patients with a low initial color index (cases 11, 28, 29, 41 and 87) the lingual and gastro-intestinal symptoms were promptly relieved by liver extract, but the blood values were not significantly improved until therapy with iron was begun. In many patients as the remission achieved by effective liver extract therapy progressed the color index and mean corpuscular volume diminished and in some instances became distinctly less than normal. In these patients

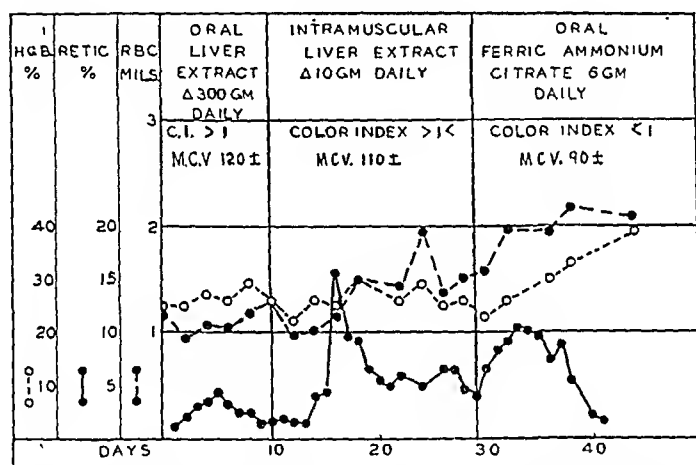


Chart 3.—A comparison of the hematopoietic effects of the daily oral administration in case 19 of liver extract derived from 300 Gm. of liver and the daily parenteral administration of the same liver extract derived from 10 Gm. of liver. The third reticulocyte response indicates the effect of ferric ammonium citrate given after the color index had become less than 1 and the mean corpuscular volume had decreased from about 120 to 90 cubic microns as a result of therapy with liver extract.

the upward progress of the blood values then became very slow despite liberal administration of liver extract. Thereupon the administration of iron salts with or without the continuation of liver extract therapy produced improvement in the blood values, occasionally associated with definite reticulocyte responses.

An illustration of the effectiveness of iron salts on 10 patients with sprue is presented in table 10. In cases 34 and 52 the color index at the beginning of the observation was close to unity, and intramuscular and oral liver extract therapy resulted only in a progressive fall of the color index at the expense of the hemoglobin, with little increase

in the number of red blood cells over periods of twenty-two days and seven weeks, respectively. The administration of 6 Gm. of ferric ammonium citrate daily then led to a definite increase in reticulocytes with a progressive increase in blood values in case 34. In case 52, as a result of iron therapy, the hemoglobin value, which had been stationary for six weeks, increased 8 per cent and the red blood cells increased over a million per cubic millimeter in fourteen days. Unfortunately, at this time the patient felt so much improved that she desisted from coming to the clinic. The other patients showed in varying degrees a progressive fall of the color index with effective liver extract therapy, a tendency of the red blood cell and hemoglobin values to become stationary and an acceleration of progress from the administration of iron. In cases 9, 17, 19 and 43 the effectiveness of the iron therapy was signaled by a definite increase in reticulocytes. The results of the observations in case 19 are graphically shown in chart 3. In case 79 the blood level was probably too high for a reticulocyte response to occur, although in this case, as in cases 2, 30 and 61, in which reticulocyte counts were not made, the augmentation of the red blood cell and hemoglobin values under therapy with iron is apparent. In numerous other instances, although less clearly demonstrable, it became apparent that the prolonged use of both liver extract and iron was necessary in order to restore the blood values to normal. The same therapeutic necessity has already been demonstrated to exist in certain cases of addisonian pernicious anemia¹⁰⁰ and in cases of pernicious anemia of pregnancy.⁶⁷ It is, moreover, possible that the deficiency of both liver extract and iron shown to exist in many of these patients was responsible for the fact that the hematopoietic responses of the patients to liver extract were usually not so marked as those of patients with addisonian pernicious anemia. This fact will be discussed under the treatment of the anemia.

The Experimental Production in Animals of Conditions Resembling Sprue by Means of Deficient Diets.—Although McCarrison¹⁹ made no references to sprue as a result of his experiments on animals, the disturbances of the gastro-intestinal tract produced by him with defective diets in pigeons, guinea-pigs and, especially, monkeys suggested to Elders¹⁸ analogies with the disturbances in patients with sprue and are even more interesting in retrospect. McCarrison summarized the symptoms in his animals as follows: "Distaste and loathing of the food, loss of appetite, depraved appetite, vomiting, diarrhea, dysentery, anemia, loss of weight, low body temperature, cardiovascular depression, asthenia, and loss of health of the skin." He made no mention of observations on the tongue but noted congestive, necrotic and inflammatory changes of the entire gastro-intestinal tract, inclusive of the

secretory elements in the mucosa. In 1917 Chittenden and Underhill¹⁰² produced an acute syndrome in dogs which they suggested might be analogous to the condition in pellagra. Necrosis and gangrene of the tongue and buccal membranes together with bloody diarrhea occurred. The upper portion of the esophagus was affected, but aside from congestion a microscopic examination of the intestinal tract revealed relatively minor changes of an atrophic character. Peas and lean meat, included in the diet, delayed the onset of the symptoms, and subsequently Underhill and Mendel¹⁰³ discovered that the syndrome could be relieved by a number of substances containing carotene. No mention of the findings in the blood was made. Goldberger and his associates¹⁰⁴ produced a somewhat similar disease in dogs fed diets resembling those of human beings with pellagra. The clinical features of the disease were those of a short illness marked by stomatitis, salivation, diarrhea and, in some instances, dermatitis. Denton¹⁰⁵ has stated that the pathologic changes resemble closely those of human pellagra. He characterized the lesions as of a degenerative type affecting the superficial connective tissue of the mucous and dermal membranes, respectively. The mouth, including the tongue, and the pharynx, esophagus, intestine and skin of the scrotum were affected. Thus, experimental evidence is not wanting that a defective diet in animals may produce lingual and gastrointestinal symptoms of an acute type together with histologic changes which have been stated to resemble the lesions in pellagra. The manifestations of the disease produced in dogs by Goldberger and his associates could be prevented or cured by use of sources of the extrinsic factor (meat or yeast)^{104b} or by liver extract.¹⁰⁶ It appears to us, however, that if the cutaneous lesions are excepted the resemblance of these conditions to pellagra is no greater than their resemblance to sprue.

102. Chittenden, R. H., and Underhill, F. P.: The Production in Dogs of a Pathological Condition Which Closely Resembles Human Pellagra, *Am. J. Physiol.* **44**:13 (Aug.) 1917.

103. Underhill, F. P., and Mendel, L. B.: A Dietary Deficiency Canine Disease—Further Experiments on the Diseased Condition in Dogs Described as Pellagra-Like by Chittenden and Underhill and Possibly Related to So-Called Black Tongue, *Am. J. Physiol.* **83**:589 (Jan.) 1928.

104. (a) Goldberger, Joseph, and Wheeler, G. A.: Experimental Black Tongue of Dogs and Its Relation to Pellagra, *Pub. Health Rep.* **43**:172 (Jan. 27) 1928. (b) Goldberger, Joseph; Wheeler, G. A.; Lillie, R. D., and Rogers, L. M.: A Further Study of Experimental Blacktongue with Special Reference to the Blacktongue Preventive in Yeast, *ibid.* **43**:657 (March 23) 1928.

105. Denton, James: A Study of the Tissue Changes in Experimental Black Tongue of Dogs Compared with Similar Changes in Pellagra, *Am. J. Path.* **4**:341 (July) 1928.

106. Goldberger, Joseph, and Sebrell, W. H.: The Blacktongue Preventive Value of Minot's Liver Extract, *Pub. Health Rep.* **45**:3064 (Dec. 12) 1930.

In the experiments so far cited little if any attention was paid to possible changes of the blood. In 1932 Wills and Billimoria¹⁰⁷ reported the production in young monkeys of a macrocytic type of anemia with megaloblastic hypertrophy of the bone marrow apparently curable with marmite, a preparation of autolyzed yeast, or with liver extract. This anemia resembled the macrocytic anemia of pregnant women in India and was curable by the same therapeutic agents.⁶³ The diet of the monkeys was based on the usual diet of these patients. No mention of lingual symptoms was made; diarrhea occurred in one monkey. The suggestion afforded by the observations made in Puerto Rico caused Rhoads to become interested in the possible resemblances between black tongue in dogs and sprue. Rhoads and Miller^{52b} placed dogs on diets resembling those used by Goldberger and his associates^{104a} in the production of black tongue. After about six weeks changes in the mouth and tongue were observed. Atrophy of the lingual papillae of the anterior and lateral aspects of the tongue occurred. Subsequently irregular diarrhea, occasionally accompanied with the passage of blood, developed. Periods of semisolid voluminous yellow stools alternated with periods of normal stools. Marked loss of weight occurred, although the diet was taken fairly well except when stomatitis and salivation were severe. By means of short intervening periods of normal diet the fatal outcome was delayed. As time passed anemia developed, which was, in certain animals, macrocytic. The extent and degree of activity of the femoral bone marrow became markedly increased, and in certain animals the hyperplasia was predominantly megaloblastic. Gastric anacidity occurred as a terminal event in a few animals. Yeasts were cultivated from the stools of about 10 per cent of the affected animals. Thus, in many respects the clinical picture and findings in the blood and bone marrow were similar to those described as occurring in sprue.

The symptoms and the anemia could be prevented or cured by a diet supplemented with sources of vitamin B₂ (G) or some closely related substance. Liver extract was also an effective curative agent when administered orally but not when injected parenterally. The failure to improve with parenterally administered liver extract may be due, as Rhoads and Miller have suggested, to specie differences between man and the dog, mentioned also by others.¹⁰⁸ The effectiveness of

107. Wills, Lucy, and Billimoria, H. S.: Studies in Pernicious Anaemia of Pregnancy: V. Production of a Macrocytic Anaemia in Monkeys by Deficient Feeding, *Indian J. M. Research* **20**:391 (Oct.) 1932.

108. Strauss, M. B., and Castle, W. B.: Amount of Material Effective in Pernicious Anemia Present in Dog Liver, *Proc. Soc. Exper. Biol. & Med.* **31**: 360 (Dec.) 1933. Ivy, A. C.; Richter, O.; Meyer, A. F., and Greengard, H.: The Relation of Gastrectomy to Anemia: On the Presence of the Substances Effective in Pernicious Anemia in Canine Stomach and Liver, *Am. J. Digest. Dis. & Nutrition* **1**:116 (April) 1934.

autolyzed yeast and liver extracts administered by mouth, however, paralleled to a significant degree the results of the observations of Wills on the macrocytic anemia of pregnant women in India and of our observations in Puerto Rico on tropical sprue, as described later. It thus appears to be at least as reasonable to claim that there is a resemblance of the canine disorder produced by Rhoads and Miller to sprue as to pellagra.

In animals fed deficient diets there may also develop abnormal neurologic signs and pathologic lesions of the central nervous system resembling those sometimes seen in sprue. Cowgill¹⁰⁹ produced, by feeding dogs diets deficient in vitamin B, acute "polyneuritis" associated with so much spasticity as to suggest involvement of the central nervous system to Gildea, Kattwinkel and Castle.¹¹⁰ With the same diet but with special attention to rendering the condition chronic these authors produced degenerative changes in the central nervous system suggestive of combined system disease. Subsequently, Zimmerman and his co-workers¹¹¹ were able to confirm these findings in dogs by using diets deficient only in vitamin B₂ (G). Crane-Lillie and Rhoads¹¹² found evidence of similar lesions in certain of the dogs studied by Rhoads and Miller.

Although the morphologic changes of the tongue, stomach and intestines of the animals which have been described suggest the possibility that physiologic disturbances known to be related to the production of macrocytic anemia accompany such lesions, it remained for Miller and Rhoads¹¹³ to demonstrate this. In experiments on pigs these authors showed that the intrinsic factor of the gastric juice of normal animals could be caused to disappear by feeding them deficient diets similar to those used in their former experiments on dogs. This important fact became known when it was shown that the gastric juice of the

109. Cowgill, G. R.: A Contribution to the Study of the Relation Between Vitamin-B and the Nutrition of the Dog, *Am. J. Physiol.* **57**:420 (Oct.) 1921.

110. Gildea, E. F.; Kattwinkel, E. E., and Castle, W. B.: Experimental Combined System Disease, *New England J. Med.* **202**:523 (March 13) 1930.

111. Zimmerman, H. M., and Burack, Ethel: Studies on the Nervous System in Deficiency Diseases: II. Lesions Produced in the Dog by Diets Lacking the Water-Soluble, Heat-Stable Vitamin B₂ (G), *J. Exper. Med.* **59**:21 (Jan.) 1934.

112. Crane-Lillie, Margaret, and Rhoads, C. P.: Pathology of the Central Nervous System in Canine Black Tongue, *Arch. Path.* **18**:459 (Oct.) 1934.

113. Miller, D. K., and Rhoads, C. P.: The Experimental Production of Loss of Hematopoietic Element of the Gastric Secretion and of the Liver in Swine with Achlorhydria and Anemia, *J. Clin. Investigation* **14**:153 (March) 1935.

affected animals after incubation with autolyzed yeast was not effective in producing hematopoietic responses in patients with typical pernicious anemia. On the other hand, immediately thereafter in the same patients the gastric juice of normal pigs was active in promoting the formation of blood after incubation with autolyzed yeast, as was previously shown to be true of normal human gastric juice in similar observations on patients with pernicious anemia.⁶⁴ These experiments on pigs fed a deficient diet offer an explanation for the origin of the defect of the intrinsic factor observed in certain patients with sprue. The defective diets responsible for this result in the pigs produced also stomatitis, gastric anacidity, diarrhea, both macrocytic and microcytic anemia and in some instances neurologic disturbances.¹¹³ Both varieties of anemia were associated with a megaloblastic type of hyperplasia of the bone marrow resembling that observed in sprue. As in sprue, the macrocytic anemia of the pigs and the neurologic disturbances responded to the intramuscular injection of liver extract. Finally, in contrast to the well known activity of normal pig liver, the livers of severely affected animals were shown not to contain substances hematopoietically active in patients with pernicious anemia. This demonstration parallels the observation which was made on the liver of a patient who died of sprue (case 81). Thus, the symptomatic, morphologic and physiologic features of the syndrome produced in pigs by defective diets are very similar to those of human sprue.

THE INFECTIOUS THEORY OF THE CAUSE OF SPRUE

In contrast to the facts outlined in support of the deficiency theory of the origin and later manifestations of sprue and its anemia, the infectious theory has little supporting evidence. Even if it is supposed that some type of infection of the alimentary tract is responsible for the lingual and gastro-intestinal manifestations of sprue, the problem of the origin of the anemia cannot be related to the infection without the interpolation of factors of deficiency. In vitro, at least, the addition of liver extract to yeast cultures on synthetic mediums has a remarkable accelerating action on growth. Since it is thus the reverse of an inhibiting agent, it is difficult to understand why the symptoms referable to the tongue and intestinal tract can be so readily abolished by an injection of liver extract if these disturbances are due to an infection.

In the opinion of Manson-Bahr and Willoughby,³⁶ much of the large amount of work on sprue during the past ten years from the bacteriologic point of view has only negative value. These authors, however, mentioned certain specific infections of the alimentary tract which may predispose to the development of the disease. Their analysis of the

previous illnesses of this type in the history of patients with sprue is as follows:

Previous Illnesses	Percentage
Diseases affecting the alimentary tract	40.5
Proved amebic dysentery	32.0
Suspected amebic dysentery	
Typhoid and paratyphoid	4.5
Hill diarrhea	2.0
Diarrhea: unclassified	1.0
Bacillary diarrhea	1.0

In this connection it is interesting to recall that diarrheal conditions are commonly associated with anemia¹¹⁴ and deficiency diseases of other types¹¹⁵ and may follow a wide variety of noninfectious intestinal lesions.¹¹⁶ Mackie, Goré and Wadia¹⁷ were unable to isolate bacteria recognized to be intestinal pathogens from the alimentary tract of 51 consecutive patients with sprue. In a later paragraph Manson-Bahr and Willoughby commented on the common observation that chronic alcoholism results in an acute or particularly intractable form of sprue. The relationship of dietary deficiency to "alcoholic" polyneuritis has recently been emphasized by Minot, Strauss and Cobb,¹¹⁷ who among 57 patients with the latter condition observed pellagra in 14, edema associated with protein deficiency in several and hypochromic anemia in others. Complete gastric anacidity was observed in 21 of 43 patients appropriately examined. Spies and DeWolf¹¹⁸ and Zimmerman, Cohen

114. Keefer, Huang and Yang.⁹⁰ Bennett, Hunter and Vaughan.⁹³

115. Barnes, J. M.: Typical Pellagra Syndrome Developing in Patients with Chronic Ulcerative Colitis While Under Hospital Treatment, *Ann. Clin. Med.* **4**:552 (Jan.) 1926. Keefer, C. S., and Yang, C. S.: The Treatment for Secondary Anemia: A Study of the Results in One Hundred and Twenty-Six Cases, *Arch. Int. Med.* **48**:537 (Oct.) 1931. Jones, C. M.: Peripheral Complications of Ulcerative Colitis, *M. Clin. North America* **16**:919 (Jan.) 1933.

116. Urmey, T. V.; Ragle, B. H.; Allen, A. W., and Jones, C. M.: Beriberi Secondary to Short-Circuited Small Intestine, *New England J. Med.* **210**:251 (Feb. 1) 1934. Turner, R. H.: Pellagra Associated with Organic Disease of the Gastro-Intestinal Tract, *Am. J. Trop. Med.* **9**:129 (March) 1929. Strauss, M. B.: The Rôle of the Gastro-Intestinal Tract in Conditioning Deficiency Disease: Significance of Digestion and Absorption in Pernicious Anemia, Pellagra and "Alcoholic" and Other Forms of Polyneuritis, *J. A. M. A.* **103**:1 (July 7) 1934.

117. Minot, G. R.; Strauss, M. B., and Cobb, Stanley: "Alcoholic" Polyneuritis; Dietary Deficiency as a Factor in Its Production, *New England J. Med.* **208**:1244 (June 15) 1933.

118. Spies, T. D., and DeWolf, H. F.: Observations on the Etiological Relationship of Severe Alcoholism to Pellagra, *Am. J. M. Sc.* **186**:521 (Oct.) 1933.

and Gildea¹¹⁹ have stated the etiologic importance of dietary deficiency in the frequent relationship of alcoholism to pellagra. Thus, by analogy with other deficiency diseases, dysentery, diverse intestinal disorders and chronic alcoholism are precisely the types of preceding illness which one would expect to find if defective nutrition is a predisposing cause of sprue. Hence, this type of evidence is quite as much in favor of dietary deficiency as of an infection as the predisposing cause of certain cases of sprue.

Kohlbrugge⁹ originally suggested the etiologic rôle of yeastlike organisms in sprue. Space permits only a cursory review of the contradictory evidence on this subject. The results of cultural¹²⁰ and immunologic studies¹²¹ have been extremely variable. Without a dietary regimen therapy by means of vaccines of these organisms has not been shown to be efficient to a significant degree.¹²² Ashford, who did much to develop the hypothesis of yeast infection with which the strain of *Monilia* bearing his name was identified,¹⁴ now considers sprue as an infection with *Monilia psilosis* made possible on a soil prepared by "nutritional unbalance."¹⁵ He⁸¹ found the scrapings of the tongue or the feces of 75 per cent of 225 patients with sprue positive for *M. psilosis*, whereas those of only 1.3 per cent of 223 patients with conditions not suggestive of sprue contained the organism. On the other hand, Mackie and Chitre^{16a} found *M. psilosis* (Ashfordi) in only 40 per cent of cases of sprue in Bombay, and the organism was recovered with equal frequency from patients with other intestinal diseases, from healthy men and from animals. *Monilias* cultivated from patients with sprue by Ashford could not be distinguished by Nye, Zerfas and Cornwell¹²³ from yeastlike fungi isolated from the membrane or sputum of patients with typical thrush or from organisms frequently found in the human gastro-intestinal tract in a variety of diseases and occasionally in normal persons.

119. Zimmerman, H. M.; Cohen, L. H., and Gildea, E. F.: Pellagra in Association with Chronic Alcoholism, *Arch. Neurol. & Psychiat.* **31**:290 (Feb.) 1934.

120. Bahr.¹² Ashford.¹⁴ Mackie and Chitre.^{16a}

121. Michel, Carl: A Study of Toxins and the Serological Reactions in Sprue, *Am. J. M. Sc.* **154**:177 (Aug.) 1917. Fairley, N. H., and Jasudasan, F.: An Investigation of the Value of the Complement Reaction in Sprue Utilizing *Monilia Psilosis* (Ashfordi) as Antigen, *Indian J. M. Research* **16**:861 (April) 1929.

122. Michel, Carl: On the Use of a *Monilia* Vaccine in the Treatment of Sprue, *J. Infect. Dis.* **22**:53, 1918. Ashford.⁸¹

123. Nye, R. N.; Zerfas, L. G., and Cornwell, M. A.: The Presence and Importance of Yeastlike Fungi in the Gastrointestinal Tract in Pernicious Anemia, in Other Diseases and in Normal Individuals, *Am. J. M. Sc.* **175**:153 (Feb.) 1928.

Fatal lesions can undoubtedly be produced in laboratory animals by the intravenous¹²⁴ and intraperitoneal¹²⁵ injection of yeastlike organisms isolated from the stools of patients with sprue. Nye, Zervas and Cornwell,¹²⁶ however, believe that the *Parasaccharomyces* A group of fungi, regardless of their source, are pathogenic for rabbits if intravenously injected, the cause of death being invariably uremia. Other groups of yeastlike organisms isolated from the alimentary tract of man were found to be nonpathogenic on intravenous injection into rabbits. On the other hand, despite the reports of success by others,¹²⁷ these authors¹²⁶ found that the oral administration of fresh cultures of *Parasaccharomyces* A to guinea-pigs on a normal diet did not produce gastro-intestinal lesions. Nye and his co-workers¹²⁶ suggested that the importance of these organisms as infectious agents is in conditions of lowered resistance. After a study of the literature and as a result of experiments with monkeys, Mackie and Chitre^{16b} concluded that sprue had not been produced in monkeys or other laboratory animals by means of organisms. Elsewhere^{16a} they conceded only that infection with yeasts may contribute to the production of abdominal distention, intestinal flatulence and frothy stools in sprue.

Our few observations on this controversial subject bear out the negative conclusions. Systematic cultures of the stools of patients with sprue were made, through the cooperation of Dr. Amerigo Pomales, on Sabouraud's medium. The stools of 28 of the 56 patients so examined were found to contain yeastlike fungi on one or more occasions. A parallel series of cultures on the stools of 46 patients with hookworm infection and hypochromic anemia yielded positive results on one or more occasions for only 13 patients. Of 15 patients with sprue and gastric anacidity, 11 had positive cultures for yeastlike organisms. This higher incidence of positive cultures in achylic subjects bears out the observations of Nye and his associates.¹²³ On the contrary, of 6 patients with hookworm infection and gastric anacidity, only 1 had yeasts in the stool. The results of the observations for individual patients are given in table 1.

124. (a) Ashford, B. K.: Studies in Moniliasis of the Digestive Tract in Porto Rico, *Am. J. M. Sc.* **150**:680 (Nov.) 1915. (b) Smith, L. W.: The Rôle of *Monilia Psilosis* (Ashfordi) in Experimental Sprue Including Mycologic Observations on Twenty-One Strains of *Monilia*, *J. A. M. A.* **83**:1549 (Nov. 15) 1924.

125. Smith.^{124b} Mackie and Chitre.^{16a}

126. Nye, R. N.; Zervas, L. G., and Cornwell, M. A.: The Pathogenicity of Yeastlike Fungi Isolated from the Human Gastrointestinal Tract, *Am. J. M. Sc.* **178**:515 (Oct.) 1929.

127. Browne, D. C.: The Effects Produced in the Rabbit by Feeding Cultures of *Monilia Psilosis*, *Proc. Soc. Exper. Biol. & Med.* **24**:873 (June) 1927. Foot-note 124.

The reported experiments on the pathogenicity of yeastlike organisms in animals were not sufficiently convincing to suggest danger in an assay on man. Accordingly, strains were isolated from the stools of 7 patients with severe sprue and were grown in dextrose broth for forty-eight hours. After the flasks were shaken, 100 cc. of the turbid contents was ingested three times daily for ten days by 2 normal subjects who had resided in Puerto Rico for six months. No symptoms were produced immediately or subsequently. In a patient with mild sprue and lingual and intestinal symptoms similar doses of the broth cultures were not observed to have any objective effect on the symptoms and signs already present. These observations at least offer no additional support to the idea that sprue is dependent on the presence of yeastlike organisms.

OBSERVATIONS CONCERNING THE TREATMENT OF SPRUE

The practice of prescribing a diet for any condition with gastro-intestinal symptoms is almost axiomatic in the lay and medical minds. To this principle the treatment of sprue with a dietary regimen including meat, milk or fruit has not been an exception. Benefit has also been ascribed to liver soup since its introduction by Sir Patrick Manson²⁵ in 1883. Nevertheless, the recent emphasis placed on intensive feeding of liver and liver extract in pernicious anemia has been carried over to the treatment of sprue largely as a method of combating the anemia.¹²⁸ Thus, although the oral administration of certain liver extracts¹²⁹ and stomach preparations⁷⁰ has been noted to produce hematopoietic effects in cases of sprue, some type of diet has usually been prescribed for the control of the diarrhea. The benefit to be derived from liver therapy in pernicious anemia is, however, not confined to the effect on the blood. Liver extract also affects favorably the lingual, gastro-intestinal and neurologic manifestations. As yet, little attention seems to have been paid to similar possibilities in the treatment of sprue. Recently Manson-Bahr and Willoughby³⁶ wrote: "The cure of sprue depends upon the administration of a nutritious and easily assimilable diet with the addition of protein and liver in order to stimulate the haemopoietic functions of the bone marrow."

EFFECT OF LIVER EXTRACTS ON THE LINGUAL AND GASTRO- INTESTINAL SYMPTOMS

Our investigations indicate a most regular and striking action of certain liver extracts effective in pernicious anemia on the lingual and gastro-intestinal symptoms of sprue. Since the patients were maintained

128. Ashford.²⁴ Manson-Bahr and Willoughby.³⁶

129. Bloomfield and Wyckoff.²² Suárez.^{25a}

on a basal diet high in carbohydrate, containing no meat, eggs or fruit and very little milk, it is possible clearly to evaluate the effectiveness of the liver extract therapy. On the other hand, it is difficult to present graphically the evidence of improvement of the symptomatology in this direction in a quantitative fashion, as is possible in showing the improvement of the blood values. No particular observations of the effect of diets usually prescribed for sprue were made except from the point of view of the hematopoietic effects. Many of the patients treated with liver extract had, however, been maintained in the past on special diets or were actually adhering to diets at the time of admission to the hospital with severe symptoms and marked anemia. In some of these patients orally administered liver extract was effective in controlling lingual and gastro-intestinal symptoms, but the majority of the patients were not remarkably improved until treatment by the parenteral route was instituted. The usual initial dosage was the amount of liver extract derived from 50 or 100 Gm. of liver given by weekly injections or the amount derived from 10 Gm. of liver injected daily. Under this therapy lingual symptoms were invariably entirely relieved within a week, and diarrhea was usually greatly diminished or even abolished within a similar time. The epigastric distress and flatulence were correspondingly improved. Within two weeks the stools were usually formed. Occasionally the relief of vomiting or of profuse diarrhea was effected within twenty-four hours. At the same time the sense of well-being and the appetite were rapidly regained, and weight and strength were gradually augmented. These effects parallel the dramatic clinical results observed in the remission in pernicious anemia produced by adequate liver extract therapy. Nevertheless, subsequent experience¹³⁰ indicated that in a few cases of sprue larger injections of liver extract are necessary to produce initial improvement in the diarrhea, especially when the condition is of long standing. The statement that the successful treatment of pernicious anemia with liver extract depends on giving doses of the material adequate for the particular patient¹³¹ holds equally in the treatment of sprue. During a continued experience with sprue since these observations were made, a special diet has been prescribed in few instances. In such cases it is possible that the initial daily administration of large amounts of liver extract intravenously, as was done in other instances of resistance to therapy,¹³⁰ would have controlled the situation without diet. After the initial improvement it has usually been found possible to maintain

130. Rhoads, C. P., and Miller, D. K.: Intensive Liver Extract Therapy of Sprue, *J. A. M. A.* **103**:387 (Aug. 11) 1934.

131. Minot, G. R., and Castle, W. B.: The Adequate Treatment of Anemia, *Ann. Int. Med.* **5**:159 (Aug.) 1931.

the patient free from sore tongue and diarrhea by injections at weekly intervals of liver extract derived from 50 to 100 Gm. of liver. In several instances the omission of liver extract therapy for a period of two weeks was sufficient to produce a recrudescence of sore tongue and looseness of the bowels, which were promptly abolished by the resumption of regular therapy. As in cases of pernicious anemia, the needs of the individual patients vary greatly, especially with oral therapy with liver extract. This variability in cases of sprue is even more prominent, probably because of the greater incidence of intestinal impermeability. Improvement from therapy with orally administered liver extract²³ or stomach preparations⁷⁰ can undoubtedly be obtained in certain cases. The use of diets containing sources of the extrinsic factor (meat, eggs) or the use of autolyzed yeast will probably not be beneficial unless the intrinsic factor is present in the gastric contents and unless intestinal absorption is adequate. Therefore, both for economic and for medical reasons the parenteral administration of liver extracts is the method of choice, certainly in patients in severe relapse. It is obvious that if irreversible anatomic changes in the intestines have occurred as a result of the chronicity or complications of sprue, the symptoms in the alimentary tract may not be entirely relieved. The extreme of this situation is probably illustrated by the persistent diarrhea and subsequent death of patient 57, in spite of an excellent hematopoietic response. With the availability of effective liver extracts for parenteral use we believe that the fundamental element in the treatment of the lingual and gastro-intestinal features of sprue is no longer a special diet but persistence in the administration of the amount of liver extract adequate for the particular patient.

TREATMENT OF THE ANEMIA, ESPECIALLY WITH PARENTERALLY ADMINISTERED LIVER EXTRACT

The treatment of the anemia of certain patients with sprue by diets containing meat and milk has become well recognized.¹³² The relatively slight hematopoietic effects of the daily addition of 300 Gm. of meat and 1,500 cc. of milk to the basal diet of 9 patients have been discussed, and the results have been set forth in table 5. From the evidence it is seen that this mode of therapy will be hematopoietically effective only when the intrinsic factor is present in the gastric contents and absorption from the intestinal tract is adequate. It is thus evident, as others have found, that such diets cannot be expected to produce significant effects on the blood with regularity. In subsequent periods of observation on 7 of these 9 patients liver extract was administered both orally and parenterally. The details of these observations are given

132. Ashford.²⁸ Manson.³⁵ Manson-Bahr and Willoughby.³⁶

TABLE 11.—Results of Parenteral Administration of Liver

	L. E. Δ 10 i.m. Daily Case 6.			L. E. Δ 100 i.m. Every 10 Days Case 8			L. E. Δ 10 i.m. Daily Case 16			L. E. Δ 10 i.m. Daily Case 33			L. E. Δ 10 i.m. Daily Case 36			L. E. Δ 100 i.m. Once Case 43			L. E. Δ 100 i.m. Every 10 Days Case 51		
	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent	Red Blood Cells, Millions	Hemoglobin, per Cent	Reticulocytes, per Cent
Days																					
0	1.30	33	1.4	0.72	23	6.0	1.23	31	1.4	2.30	48	2.8	0.69	21	0.4	0.55	17	0.6	0.72	13	2.2
2	1.27	36	1.0	0.81	25	6.4	1.31	29	1.0	1.68	45	1.4	0.89	25	0.2	0.65	18	...	0.94	16	4.4
4	1.17	40	2.8	1.16	32	39.4	1.53	35	1.4	1.4	0.90	23	0.4	0.68	18	1.0	0.89	19	21.2
6	1.54	47	10.8	1.52	35	47.6	1.49	31	5.2	1.58	48	4.4	0.87	26	6.0	0.56	23	17.0	1.13	25	38.0
8	1.72	47	12.0	1.88	41	19.4	1.82	39	12.0	1.66	52	11.0	1.14	31	12.6	0.80	25	14.8	1.45	31	6.8
10	2.06	50	4.4	1.86	40	15.4	1.95	50	8.0	1.13	37	10.0	0.79	25	9.2	1.71	35	5.6
12	2.15	53	2.2	1.90	40	4.8	2.20	40	8.4	1.44	39	3.6	0.79	26	5.4	1.81	36	7.6
14	2.37	47	7.0	2.08	57	1.06	27	4.8	2.32	44	12.0
16	2.14	46	7.8	2.43	48	2.4	2.12	59	0.72	26	9.0	2.48	44	17.4
18	2.10	44	2.0	1.23	30	7.0	2.83	53	5.6
20	3.07	61	5.2	2.11	43	4.2	2.73	65	1.50	34	8.0	2.72	55	4.8
22	2.25	42	5.2	1.65	33	6.0	2.96	60	4.2
24	2.30	43	3.2	1.45	35	6.6
26	1.93	40	3.0	1.65	35	3.8
28	3.76	74	...	2.45	43	4.2	3.12	74	1.71	35	4.6	2.96	59	3.4
Weeks																					
5	3.66	68	1.0	3.23	70	2.24	37	2.0	3.93	73	2.0
6	3.79	76	1.6	3.06	72	4.00	67	2.2
7	3.84	76	3.27	78	1.0	5.02	70	1.0
8	3.70	79	3.00	72	5.11	73	...
9	3.95	80	3.75	73
10	3.84	86	3.27	76	5.25	83	...

in table 5, and others are shown in tables 4 and 6. In certain patients the orally administered liver extract produced a rise in the reticulocyte count, but in other patients such a response first appeared or was repeated after the liver extract was administered parenterally. Since the publication of the preliminary report²⁷ of these studies, confirmatory results of the greater hematopoietic effects of parenterally administered liver extracts in cases of sprue have been made by Rogers and Cooke,¹³³ van der Scheer¹³⁴ and others.

The details of many observations on the effect of parenterally administered liver extract are shown in tables 4, 5, 6 and 11. An inspection of the data in table 12 for the highest percentage of reticulocytes obtained in each of 17 patients from the daily oral administration of liver extract derived from 300 Gm. of liver shows clearly that the responses, except in case 53, were less than would be expected from comparable therapy in similar patients with pernicious anemia. In 3 additional patients (cases 78, 90 and 92) the daily oral administration

133. Rogers, Leonard, and Cooke, W. E.: Resistant Sprue Anaemia Yielding to Intravenous Liver Extract, *Brit. M. J.* **1**:272 (Feb. 13) 1932.

134. van der Scheer, A.: Parenterale leverttoediening bij tropische spruw, *Nederl. tijdschr. v. geneesk.* **77**:163 (Jan. 14) 1933.

Extract in Dosage Maximally Effective in Pernicious Anemia

L. E. Δ 100 l.m. Every 10 Days	L. E. Δ 50 l.m. Daily	L. E. Δ 50 l.m. Daily	L. E. Δ 10 l.m. Daily	L. E. Δ 100 l.m. Every 7 Days	L. E. Δ 10 l.m. Daily	L. E. Δ 100 l.m. Every 10 Days
Case 57	Case 64	Case 65	Case 71	Case 73	Case 74	Case 75
Red Blood Cells, Millions	Red Blood Cells, Millions	Red Blood Cells, Millions	Red Blood Cells, Millions	Red Blood Cells, Millions	Red Blood Cells, Millions	Red Blood Cells, Millions
Hemoglobin, per Cent	Hemoglobin, per Cent	Hemoglobin, per Cent	Hemoglobin, per Cent	Hemoglobin, per Cent	Hemoglobin, per Cent	Hemoglobin, per Cent
Reticulocytes, per Cent	Reticulocytes, per Cent	Reticulocytes, per Cent	Reticulocytes, per Cent	Reticulocytes, per Cent	Reticulocytes, per Cent	Reticulocytes, per Cent
0.75 25 6.6	0.60 18 0.6	0.68 17 3.8	2.26 60 4.0	1.33 36 2.0	1.23 35 1.0	0.79 23 2.4
0.76 27 10.4	0.65 18 0.4	0.64 19 4.0	1.49 54 0.1	1.29 35 2.4	1.02 32 2.8	0.69 19 2.0
0.88 27 16.0	0.69 18 9.0	0.88 27 10.0	1.72 53 1.8	1.28 37 4.6	1.05 34 9.2	0.66 21 13.2
1.04 36 33.8	0.88 23 21.2	1.03 26 17.2	1.95 55 4.8	2.10 45 17.4	1.22 39 26.8	0.78 24 35.8
1.22 35 40.8	1.26 23 26.6	1.42 30 7.6	2.11 60 14.8	2.20 51 12.2	1.75 42 12.0	1.40 29 21.6
1.44 39 8.0	1.58 40 7.0	1.55 29 4.6	2.32 62 10.6	2.29 48 5.4	2.10 50 3.8	1.53 35 8.4
1.41 36 9.2			2.45 61 3.6	2.36 55 4.8	2.08 50 6.2	1.57 35 9.0
1.63 35 10.2	L. E. Δ 100 Every 7 Days	2.71 58 3.6	2.10 54 2.6	1.83 40 3.4
			2.46 65 5.0	...	2.56 57 2.2	1.75 40 3.2
1.79 43 4.8	2.68 59 2.6	...
2.00 42 3.4	2.50 63 5.4
2.02 39 4.6	2.69 60 1.4	2.61 65 2.4	1.89 49 3.6
2.20 46 4.2	2.64 66 2.0	...	3.00 69 1.2	...
...	3.15 67
...	3.06 72 2.0
2.06 42 4.8	3.62 73 0.8	3.59 75 0.8	2.19 53 2.6
...	3.04 73 2.4	4.02 76 0.6	3.70 81 0.6	2.69 55 2.0
2.36 44 2.4	3.74 79 1.4	3.69 72	2.95 51 ...
2.33 43	3.20 76 2.4	...	4.26 86 ...	2.78 55 ...
2.58 43	2.97 78 2.0	...	4.30 87
2.52 42	3.35 80 1.8
...	3.81 82

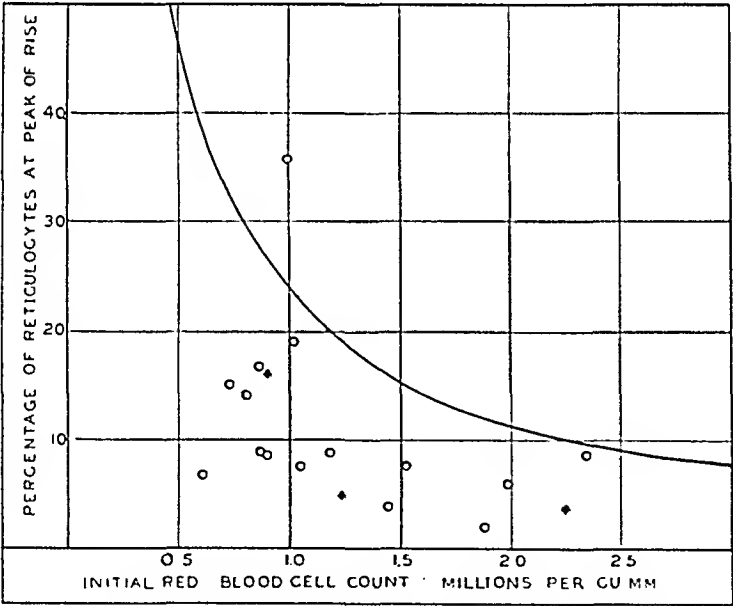


Chart 4.—The individual reticulocyte responses of 15 patients with sprue given daily by mouth liver extract derived from 300 Gm. of liver (circles), and the response of 3 patients with sprue given daily by mouth liver extract derived from 600 Gm. of liver (diamonds). The curved line indicates the average reticulocyte response expected in similarly anemic patients with pernicious anemia from the daily oral administration of liver extract derived from 300 Gm. of liver. Note that in only 1 patient with sprue was the expected response exceeded and that in most instances the responses were distinctly less than in pernicious anemia.

of liver extract derived from 600 Gm. of liver also gave distinctly submaximal reticulocyte responses. The percentage of reticulocytes at the peak of their rise for each of these 20 patients is plotted in chart 4 against the initial red blood cell count. The curved line in chart 4 is derived from the data of Minot and his associates^{33a} and represents the average response of similar patients with pernicious anemia given daily about 230 Gm. of liver, which is approximately equivalent in potency to liver extract derived from 300 Gm. of liver. Since oral therapy was

TABLE 12.—*Response of the Reticulocytes and Increase of Red Blood Cells Resulting from Therapy with Liver Extract Administered by Mouth*

Case	Initial Therapy, Liver Extract	Maximal Reticulocyte Percentage		Red Blood Cells, Millions per Cu. Mm. at 10 Day Intervals				
		Expected	Observed	0 Days	10 Days	20 Days	30 Days	40 Days
4	△300 d.*	2.26	2.10	2.56
10	△300 d.	10	8.4	2.34	2.62
15	△300 d.	15	7.2	1.52	2.00
27	△300 d.	12	5.6	1.98	2.38	2.80	3.00	3.06
32	△300 d.	23	7.4	1.04	1.18	1.47
40	△300 d.	16	3.8	1.45	1.76
44	△300 d.	25	9.2	0.90	0.91
49	△300 d.	43	6.6	0.62	0.76
53	△300 d.	24	35.8	1.00	1.24	1.91	2.05
54	△300 d.	26	8.4	0.89	0.86
55	△300 d.	20	8.8	1.17	1.28	1.63
61	△300 d.	35	15.0	0.73	0.87
62	△300 d.	2.22	2.37
68	△300 d.	13	1.8	1.88	1.93
72	△300 d.	27	16.4	0.87	1.25	1.46
78	△600 d.	44	16.0	0.90	1.47
82	△300 d.	29	14.0	0.81	0.92
83	△300 d.	23	19.0	1.02	1.34
90	△600 d.	17	3.6	2.25	2.24
92	△600 d.	33	4.6	1.24	1.00
Average number of red blood cells.....				1.35	1.52			

* △ (derived from), 300 (Gm. of liver), d. (daily).

changed to parenteral therapy after from ten to fourteen days for most of these patients, the data concerning increases in the red blood cell count are insufficient to justify conclusions. The average increase of red blood cells in the first ten days of therapy for these 20 patients was, however, only 170,000 per cubic millimeter, in contrast with an expected increase of about 600,000 for comparably anemic patients with pernicious anemia (chart 6).

In table 13 are shown data derived from observations on 18 patients given daily by intramuscular injection liver extract derived from 10 Gm. of liver, as well as data on 12 patients given the same liver extract

derived usually from 100 Gm. of liver at intervals of seven or ten days. Another patient (case 64) received the extract derived from 50 Gm. of liver daily by injection. The details of the observations on certain patients are shown in tables 4, 5, 6, 10 and 11. Table 13 shows the reticulocyte responses obtained in each patient, as well as the response to be expected in similar patients with pernicious anemia for each method of administration. In chart 5 the maximal percentage of the reticulocytes attained in each patient is plotted against the initial red blood cell count. The lower curve in the chart is derived from the data of Minot and his associates^{33a, b} for the average reticulocyte response in pernicious anemia to the daily oral administration of liver extract derived from 600 Gm. of liver. These values, given by Bethell and Goldhamer,^{33c} correspond to the average response to be expected from the daily intramuscular injection of liver extract derived from 10 Gm. of liver, according to the observations of Strauss, Taylor and Castle.⁸⁹ The upper curve in chart 5, according to Bethell and Goldhamer, corresponds to the average expected response of the reticulocytes in pernicious anemia resulting from a single intravenous injection of liver extract derived from 100 Gm. of liver. The individual responses plotted in chart 5 show that the reticulocyte response expected in pernicious anemia was not attained by either method of parenteral administration in any patient with sprue. In many instances the responses were greatly inferior to those expected in comparably anemic patients with pernicious anemia.

In table 13 are also shown the red blood cell values of each patient plotted at successive ten day intervals after the beginning of parenteral liver extract therapy. The bold face figures indicate the periods during which certain patients were also receiving iron. At the bottom of the table are shown the average red blood cell counts for the whole group at ten day intervals.

These average red blood cell counts are plotted against days in chart 6 in the solid line with solid dots. From the information given by Isaacs, Sturgis, Goldhamer and Bethell,^{88b} a solid line with open circles connecting four points on the chart has been drawn to indicate the increases of the red blood cell count observed by these authors in 10 cases of pernicious anemia with an average initial red blood cell count of 1,420,000 per cubic millimeter. Their patients were given weekly intravenous injections of the extract derived from 100 to 125 Gm. of liver. The average weekly increase during the first two weeks was 573,000 per cubic millimeter. In fifty days the average red blood cell count had increased to 4,290,000 per cubic millimeter. The broken line extending over a period of thirty days represents the results of the

observations of Minot and his co-workers^{33b} on 24 patients with uncomplicated pernicious anemia given daily by mouth liver extract derived from 500 or 600 Gm. of liver. The average initial red blood cell count of these patients was 1,200,000 per cubic millimeter. At the end of thirty days it had reached an average of 3,800,000 per cubic millimeter. Finally, the broken line with circles represents the average increase of red

TABLE 13.—*Response of the Reticulocytes and Increase of Red Blood Cells Resulting from Therapy with Liver Extract Administered Parenterally and from the Addition of Orally Administered Ferric Ammonium Citrate (6 Gm. Daily)*

Case	Initial Therapy Liver Extract	Maximal Reticulocyte Percentage		Red Blood Cells, Millions per Cu. Mm. at 10 Day Intervals										
		Ex- pected	Ob- served	0 Da.	10 Da.	20 Da.	30 Da.	40 Da.	50 Da.	60 Da.	70 Da.	80 Da.	90 Da.	
4	Δ 10 d.*	10.0	5.6	2.34	2.68	2.58	2.85	3.10	3.36	3.60	3.95	4.10	4.18	
5	Δ 10 d.	17.7	7.2	1.76	2.83	2.96	
6	Δ 10 d.	26.5	12.0	1.30	2.06	2.30	2.90	3.54	3.95	4.00	4.13	4.33	4.50	
8	Δ 100	54.1	47.6	0.80	1.90	3.07	3.76	3.66	3.79	3.84	3.70	3.95	4.07	
12	Δ 10 d.	8.5	3.0	2.49	2.53	2.82	3.44	
14	Δ 10 d.	9.0	6.6	2.46	2.65	
16	Δ 10 d.	26.3	13.2	1.31	2.20	2.25	2.49	3.24	
19	Δ 10 d.	27.0	15.8	1.28	1.50	1.58	
30	Δ 100 w.*	38.5	22.2	1.31	2.01	2.60	2.80	2.60	3.30	3.40	3.76	3.68	3.85	
31	Δ 10 d.	28.7	9.8	1.21	1.32	2.55	3.13	3.63	3.60	4.18	4.33	4.60	
33	Δ 10 d.	22.7	11.0	1.48	1.95	2.73	3.19	3.12	3.22	3.53	3.20	3.36	3.51	
36	Δ 10 d.	38.0	12.6	0.90	1.13	1.22	1.22	1.20	1.71	1.90	2.62	2.60	
37	Δ 10 d.	18.1	5.9	1.74	1.90	2.67	3.00	
40	Δ 10 d.	18.7	15.0	1.70	2.50	3.08	3.38	3.78	
43	Δ 100	61.8	17.0	0.60	0.79	1.50	2.13	2.68	3.26	3.36	
45	Δ 10 d.	15.1	8.0	1.93	2.13	3.08	3.16	3.32	3.50	3.67	3.88	3.94	4.00	
47	Δ 10 d.	16.8	5.6	1.82	2.23	2.33	2.42	2.81	3.20	3.28	3.80	
51	Δ 100, 10 d.	57.8	38.0	0.70	1.45	2.83	2.96	3.98	4.00	5.13	5.18	5.22	5.26	
57	Δ 100, 10 d.	54.1	40.8	0.80	1.41	1.73	2.36	2.33	2.58	3.03	
58	Δ 100, 10 d.	17.5	5.8	2.34	2.85	2.87	
59	Δ 100, 10 d.	43.7	25.6	1.12	1.78	2.35	3.50	
62	Δ 100 w.	2.24	2.70	3.40	3.30	3.30	
64	Δ 50 d.	61.8	26.6	0.60	1.58	2.01	2.30	2.63	2.90	2.76	3.42	
65	Δ 100 w.	58.6	17.2	0.68	1.55	2.84	3.43	3.70	4.32	4.24	
71	Δ 10 d.	15.8	14.8	1.89	2.45	2.64	3.03	3.74	3.20	3.46	3.85	
73	Δ 100 w.	39.2	17.4	1.28	2.40	2.80	3.50	4.00	
74	Δ 100 w.	44.3	26.8	1.10	2.10	2.60	3.26	3.56	3.84	4.20	4.00	4.30	4.62	
75	Δ 100, 10 d.	54.1	35.8	0.80	1.53	1.88	2.30	2.50	2.95	2.90	2.85	3.00	3.20	
79	Δ 10 d.	27.8	9.2	1.25	1.55	1.91	2.36	2.76	3.18	
86	Δ 10 d.	17.7	12.6	1.76	1.71	2.34	3.17	
88	Δ 10 d.	23.9	13.8	1.42	2.09	2.14	2.81	3.67	
90	Δ 100, 10 d.	19.5	6.0	2.24	3.07	3.39	
92	Δ 100, 10 d.	47.4	29.8	1.00	1.95	3.20	3.35	3.87	3.85	4.13	4.45	
Average number of red blood cells				1.44	2.01	2.36	2.91	3.20	3.40	3.59	3.80	3.92	4.13	

* △ (derived from), 10 (Gm. of liver), d. (daily); w. (weekly.)

The bold face figures indicate the response after the addition of ferric ammonium citrate.

blood cells in 105 unselected patients with pernicious anemia observed by Minot and Murphy²⁶ who received a diet containing daily about 200 Gm. of cooked liver.

It is evident that the average increase of erythrocytes in these patients with sprue was less than in any of the groups of patients with pernicious anemia. Had the effect of therapy with liver extract on the anemia of the two diseases been comparable the increase of erythro-

cytes should have been about as rapid as that produced by the daily oral administration of liver extract derived from 500 or 600 Gm. of liver (broken line) and probably almost as rapid as that produced by the weekly injection of the extract derived from 100 Gm. of liver (solid line and circles). As a matter of fact, it was not even as rapid as the average increase of erythrocytes of patients with pernicious anemia in response to a diet containing 200 Gm. of liver daily (broken line and circles).

The smaller rises in the number of reticulocytes and the slower gains of the erythrocyte count in response to liver extract therapy obtained in the anemia of sprue as contrasted with those achieved in addisonian

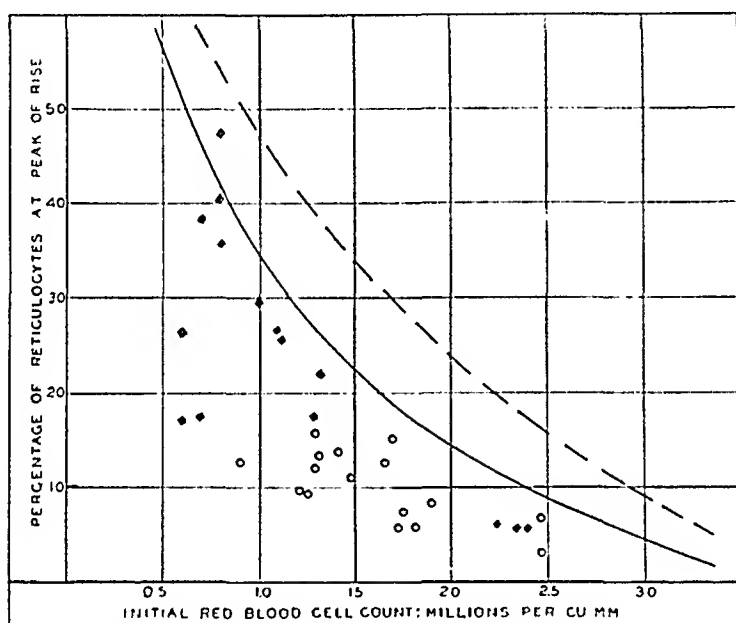


Chart 5.—The individual reticulocyte responses of 16 patients with sprue given daily by injection liver extract derived from 10 Gm. of liver (circles). The lower curve in the figure indicates the reticulocyte response to be expected from such therapy in equally anemic patients with pernicious anemia. The individual reticulocyte response of 15 patients with sprue given one or more injections of liver extract derived from 100 Gm. of liver at intervals of a week or ten days are indicated by the diamonds. The upper curve corresponds to the average reticulocyte response to be expected in equally anemic patients with pernicious anemia given by intravenous injection the extract derived from 100 Gm. of liver. Note that in no instance was a reticulocyte response attained in the patients with sprue comparable with those observed in patients with pernicious anemia.

pernicious anemia cannot be entirely explained by our observations. The possible influence of difficulty with the absorption of hematopoietic material may be partly responsible for the relatively slight effect of orally administered material on the production of reticulocytes. This explanation, however, cannot be considered pertinent when therapy is

administered parenterally. It is known that in certain patients with pernicious anemia a "double deficiency" exists in the sense that optimal formation of blood is not possible without the use of both liver extract and iron. Observations indicate that this is also true in certain patients with sprue. Initially in a few patients and in the later stages of the recovery of several of the patients, the effectiveness of iron was clearly demonstrated (table 11). The administration of both iron and liver extract from the beginning was not attempted; so it is not possible to state that the original response of the reticulocytes would have been enhanced by the combination. In the absence of such data it is possible only to speculate on the further evidence supplied by the morphology of the bone marrow. Certainly no patients were found to have a con-

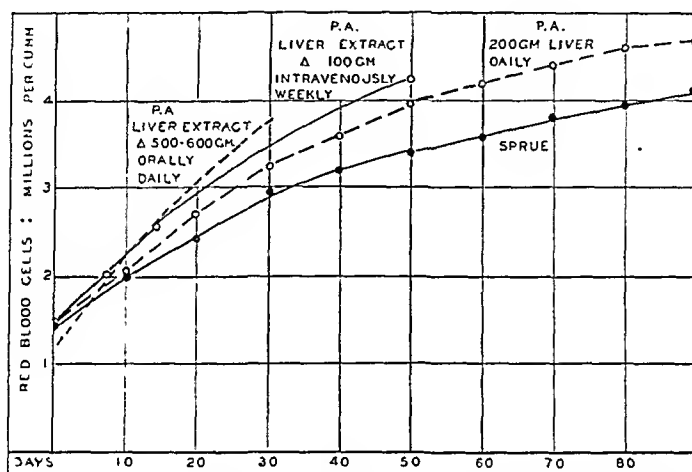


Chart 6.—The average increase of red blood cells in 33 patients with sprue with less than 2,500,000 red blood cells per cubic millimeter following parenteral therapy with liver extract in the dosage indicated in table 13. In those patients indicated in table 13, daily oral administration of 6 Gm. of ferric ammonium citrate was added. The solid line with dots indicates the results in the patients with sprue. The solid line with circles indicates the effect of the weekly intravenous injection of liver extract derived from 100 Gm. of liver on 10 patients with pernicious anemia and a comparable red cell count. The broken line, extending over a period of thirty days, indicates the average effect on 24 comparably anemic patients with pernicious anemia given daily by mouth liver extract derived from 500 to 600 Gm. of liver. The broken line with circles represents the average increase of red blood cells of 105 patients with pernicious anemia given daily about 200 Gm. of liver. Note that the average increase of red blood cells in patients with sprue was less than that in patients with pernicious anemia treated with liver or liver extract whether orally or parenterally administered.

dition in the normally active bone marrow suggesting the aplasia found in the long bones by others, nor were hematopoietic responses to the administration of liver extract lacking in any patient. It is, however, our impression that the extension of the hyperplastic marrow to the long bones in patients with sprue is not so marked or so regular as in

those with pernicious anemia. Thus, in pernicious anemia the larger amount of hyperplastic marrow available for activity after the administration of liver extract might explain the greater hematopoietic responses. The influence of infection is another factor which sometimes inhibits the response of patients with pernicious anemia to liver extract. It is hardly probable that infection sufficient to inhibit the response of the hematopoietic organs could have been present in every patient and not have been detected. The presence of yeastlike organisms in the intestinal tract was not constant in these patients, and from a survey of the work of others and of our work on this subject it is impossible to become convinced of their etiologic importance. What is certain is that in every patient not proved to have a complicating infection some degree of initial hematopoietic response to parenterally administered liver extracts effective in pernicious anemia was observed and that later progress could be accelerated in many patients by iron. Since this was accomplished without the use of the diets usually prescribed, it is clear that the use of special diets is not necessary for increasing the production of blood.

MISCELLANEOUS ASPECTS OF TREATMENT

In the observations made on 8 patients considered to have suggestive evidence of neurologic complications parenterally administered liver extract over several weeks gradually caused a decrease in the symptoms. The paresthesia became distinctly less or disappeared, and in 2 instances the gait was definitely improved. This slow improvement corresponds to that observed in patients with combined system disease and pernicious anemia.¹³⁵ In 1 patient with sprue, observed since this series of observations, two preceding attacks of profuse diarrhea associated with severe tetany with a lowered value for blood calcium had been relieved by therapy with calcium and viosterol. While this patient was under observation a moderate degree of tetany again developed, and the blood calcium was found to be 7.1 mg. per hundred cubic centimeters. Calcium lactate and viosterol again promptly abated the attack in spite of persistent diarrhea which was not checked until liver extract was given parenterally. Similar results were subsequently observed in another patient.

The progressive improvement of all aspects of these patients with sprue after the institution of therapy with parenterally administered liver extract has been described with many illustrations. Among the 92 patients there were, however, 4 deaths.

135. Ungley, C. C., and Suzman, M. M.: Subacute Combined Degeneration of the Cord: Symptomatology and Effects of Liver Therapy, *Brain* **52**:271 (Sept.) 1929. Minot and Murphy.²⁶

Patient 57 was a 67 year old Puerto Rican woman who had suffered from sprue for two years. She had profuse diarrhea and showed great emaciation. She was adequately treated with liver extract by parenteral injection and subsequently with iron. An excellent hematopoietic response occurred, as shown in table 11. Nevertheless, the patient continued to have a low grade fever, her appetite did not improve, and the diarrhea was not controlled. Tuberculous enteritis was suspected but never proved. Autopsy was not performed.

In case 76 a 34 year old Puerto Rican had suffered from sprue for ten months. Except for severe anemia he appeared to be in good condition, with little diarrhea. Attempts to administer a diet containing meat resulted in vomiting, an increase of diarrhea and sudden collapse and rise of temperature. On the day before death liver extract derived from 100 Gm. of liver was given by intramuscular injection. Autopsy revealed observations typical of sprue and disclosed multiple small abscesses of the lungs.

In case 77, a 66 year old man had suffered from sprue for three months. He was moderately anemic and emaciated and complained of cough. Examination of the lungs gave negative results. After a month of therapy with orally administered liver extract derived from 300 Gm. of liver daily, the blood values were not improved. Because of increased cough, pain in the chest and fever he was admitted to the hospital. He was then given a single injection of liver extract derived from 100 Gm. of liver, from which no reticulocyte response occurred within ten days. As he was then not improved clinically he was given half that amount of liver extract by intravenous injection daily for four days without benefit, before his death. Autopsy revealed observations typical of sprue and disclosed a single, large chronic abscess of the lung.

Patient 81 was a 62 year old Puerto Rican who had suffered from sprue for six years. He was moderately emaciated and severely anemic despite adherence to a diet for sprue. Oral therapy with autolyzed yeast was begun, but because of the patient's poor condition it was discontinued on the fourth day. A transfusion of 300 cc. of blood and a single intramuscular injection of liver extract derived from 100 Gm. of liver were given without improvement. The patient died the next day. Autopsy revealed observations typical of uncomplicated sprue.

Of the 4 patients who died, those in cases 57 and 77 were adequately treated with liver extract parenterally administered but probably had complications which were responsible for the fatal outcome. Patients 76 and 81 did not receive therapy for a sufficient length of time to regard the result as a failure of therapy with liver extract parenterally administered. In all the other patients treated parenterally with liver extract and, if necessary, with iron, clinical and hematologic improvement occurred. That the values for red blood cells and for hemoglobin were in some cases only slowly elevated is evidenced by the data already presented. In the majority of cases, however, the prompt relief of symptoms referable to the alimentary tract and the progressive increase of blood values were striking as soon as parenteral therapy with liver extract was instituted. This improvement, moreover, was produced in several instances when the failure of other methods of treatment was all too evident.

SUMMARY

The evidence for our belief that sprue is a deficiency disease closely related to addisonian pernicious anemia has been presented in detail.

The chief manifestations of both diseases consist in the disturbances of the tongue, stomach and intestines, the anemia and (rarely in sprue) the degenerative lesions of the spinal cord. These several organs are admittedly not all affected in each patient with either disease, but the characteristic manifestations of each disease are distinguishable largely by their differing intensity. In certain instances, however, it was beyond our clinical ability to decide whether the condition under observation in Puerto Rico was sprue or pernicious anemia. Especially was this true of the appearance of the tongue, the blood picture and the histologic changes in those regions of the bone marrow which were normally active.

Certain therapeutic agents relieve the lingual and gastro-intestinal manifestations, abolish the macrocytic anemia and improve the disturbances of the nervous system in both diseases. The parenteral administration of the liver fraction G of Cohn, Minot and their associates²¹ invariably relieved the "inflammation" of the tongue, as in pernicious anemia. It produced characteristic hematopoietic responses in patients with macrocytic anemia, definite but not so great as in patients with pernicious anemia. Failure of the hematopoietic activity of this liver extract on oral administration in certain patients with sprue, which had been observed by others, was confirmed but was satisfactorily explained by the demonstration of the subsequent activity of the liver extract in the same patients on parenteral administration. Slow improvement of the paresthesia and ataxia of the few patients so affected resulted from therapy with liver extract parenterally administered, as in pernicious anemia.

These analogies led to the discovery of intimate resemblances between the two diseases in respect to a disturbance of a specific reaction leading in the normal person to the production of "liver extract." It was observed that the lingual and gastro-intestinal manifestations of incipient sprue could be abolished by the administration of beef muscle or of preparations of autolyzed yeast in certain patients. In other patients this could be accomplished only after the addition of normal human gastric juice. The failure of this reaction between a food (extrinsic) and a gastric (intrinsic) factor has been repeatedly demonstrated in addisonian pernicious anemia in relapse. The acid-containing gastric contents of 2 patients with fully developed sprue and macrocytic anemia, when examined by tests such as those given patients with pernicious anemia, showed a lack of the intrinsic factor. In a third patient with a short history of sprue and little

anemia, similar tests indicated the presence of the intrinsic factor in the acid-containing and pepsin-containing gastric juice. Thus, the failure of the reaction in patients with pernicious anemia, usually due to a lack of the intrinsic factor, was produced in certain patients with sprue in an identical manner. In other patients the failure of this reaction was due to a lack of the extrinsic factor. A further analogy with addisonian pernicious anemia was observed in the relative ineffectiveness of orally administered liver extract on the anemia of certain patients with sprue. The subsequent considerable activity of parenterally administered material in these same patients was considered to suggest, but not to establish beyond question, the presence of intestinal impermeability to hematopoietic substances.

Thus, the development of sprue and its macrocytic anemia was considered to be due in different patients to the variable participation of three causes: (1) a lack of a factor (extrinsic) in the diet associated with vitamin B₂ (G) in meat, eggs and whole cereal but not as yet identified as any fraction of the vitamin B complex; (2) a failure of the secretion of a factor (intrinsic) in the normal gastric juice presumably identical with the substance usually lacking in addisonian pernicious anemia in relapse, and (3) difficulty with the absorption of the products of this reaction from the intestinal tract. The influence of dietary defect, gastric anacidity and intestinal impermeability on the intake of iron is considered to have a bearing on the defective metabolism of iron and consequent hypochromic anemia of certain patients with sprue. The possibility of the increasing influence of intestinal impermeability in the more advanced disease was pointed out. Destruction of hematopoietic substances in the gastro-intestinal tract as well as defects of their utilization within the body are also theoretically important factors.

By analogy with pernicious anemia, as a result of defects of one or more of the foregoing mechanisms of deficiency, a deficiency of "liver extract" should exist in the bodies of the patients with sprue and macrocytic anemia. This fact was proved by the demonstration that the liver of a patient who died of sprue with severe macrocytic anemia did not contain detectable amounts of the "liver extract" hematopoietically active in pernicious anemia. The same observation has been made in cases of addisonian pernicious anemia and has been regarded as evidence of the nature of the internal deficiency in that condition.

Certain authors have observed that defective diets in animals lead to marked symptoms and pathologic findings in the tongue, stomach and intestinal tract. Such symptoms, together with macrocytic anemia responding to the oral administration of a liver extract

effective in pernicious anemia, have been produced in dogs by Rhoads and Miller. Similar anemia, responding to the oral administration of a source of the extrinsic factor (Marmite) or of liver extract, has been produced in monkeys by Wills. In both kinds of animals hyperplasia of the bone marrow of a megaloblastic type was produced. The diets causing these results were in both instances deficient in vitamin B₂ (G) or substances frequently associated with it. Symptoms and pathologic changes in the central nervous system resembling combined system disease have also been produced in dogs by diets deficient in vitamin B or some related substance. Thus, the major clinical features of sprue have been produced in animals with deficient diets and the manifestations abolished by substances known to be therapeutically effective in both sprue and pernicious anemia. The observations of Ashford as well as our analysis of the diets of patients with sprue clearly favor the possibility of the existence of dietary defects similar to those of the animals. Wills' animals were actually given diets based on those of patients suffering from tropical macrocytic anemia.

Since the administration of defective diets to animals may produce not only macrocytic anemia but also profound morphologic and physiologic derangements of the alimentary tract, a cause sufficient to account for the secretory and probably for the absorptive defects of the patient with sprue is exhibited. It is likely, therefore, that the influence of a deficiency of the extrinsic factor or some related substance may originally be responsible for diminishing the intrinsic factor secreted by the stomach, as was demonstrated by the observations of Miller and Rhoads¹¹³ on pigs, or for producing other degenerative changes leading to intestinal impermeability. Thus, as has been pointed out elsewhere^{62b} in relation to pernicious anemia, a vicious cycle would be created. The original effect of a defective diet would subsequently be enhanced by the development of the defects of the alimentary tract involved in the production of macrocytic anemia. The reversal of this cycle in pernicious anemia by effective treatment with liver extract has been demonstrated by the reappearance of the intrinsic factor formerly absent from the gastric juice.^{62b} In pernicious anemia, however, aside from extirpation of the stomach or its destruction by cancer, the usual subtle process leading to a disappearance of the intrinsic factor has not been disclosed. In sprue the obvious dietary defects provide, by analogy with experiments on animals, a rational explanation of the subsequent defects of the specific functions of the alimentary tract demonstrated in patients. It would perhaps be well to borrow the information disclosed by a study of sprue and seek its application to the problems of pernicious anemia.

On the other hand, most investigators have been unable to reproduce in animals the clinical picture of sprue by the use of yeastlike organisms. The inconstancy of the finding of yeasts in the stools of patients with sprue, the lack of immunologic evidence for an etiologic relationship and the frequent occurrence of these organisms in the stools of patients lacking symptoms of sprue have been discussed. The negative effect on man of the oral administration of cultures of yeasts isolated from the stools of patients with active sprue was observed. The importance of dysentery, chronic alcoholism and noninfectious lesions of the alimentary tract in producing a variety of deficiency diseases has been reported. Thus, the predisposing influence of these conditions may be as logically interpreted on the basis of their effect on nutrition as on the basis of infection.

The alleged influence of a short residence in the tropics on the development of sprue, soon or late, remains a mystery. Nevertheless, if it results in the disease which we have observed a deficiency state must eventually be involved. We can only suggest the obligatory modification of the diet of the northern visitor, noted by Ashford, the deleterious effect of continued high temperature on the appetite which is commonly experienced and the decrease of gastric secretion which is demonstrable under these circumstances.¹³⁶ It is also possible that the occasional person who acquires sprue shortly after arrival in the tropics was already closer to "pernicious anemia" than he realized or was originally hastened into a deficiency state by the onset of some type of infectious dysentery.

The explanation of the etiology of sprue which we have advanced and in particular the analogies drawn between sprue and pernicious anemia will doubtless encounter many objections. In their respective territories the classic examples of each disease obviously differ in their clinical pictures. Yet these differences are scarcely greater than are the differences between the clinical picture of incipient sprue and that of the full-blown disease or between the aspect of a patient with severe combined system disease and little anemia and that of a patient with classic Addisonian pernicious anemia. It has been our experience to observe patients who reported leaving the tropics with symptoms typical of sprue but who on examination a few weeks later in Boston presented no obvious differences from pernicious anemia. The explanation of the varied manifestations of other deficiency diseases in man is hardly more satisfactory. From the practical point of view of

136. Bogendörfer, L., and Sell, A. R.: Ueber die Wirkung von äusseren Temperatureizen auf die Sekretionstätigkeit des Magens, *Deutsches Arch. f. klin. Med.* **169**:166, 1930.

therapy, however, these distinctions are of purely academic interest. That sprue is a close relative of pernicious anemia in its chief manifestations can scarcely be doubted by one who has had occasion to observe the remarkable benefit resulting from the parenteral administration of liver extract to severely sick patients with both diseases.

As a result of our observations on these patients and on others subsequently studied we emphasize the primary importance of the adequate treatment of the patient with sprue with parenterally administered liver extract as a method not only of combating the anemia but of controlling the lingual and gastro-intestinal manifestations of the disease. Repeated experience has shown that when therapy including diet or orally administered liver extract has failed the results of parenterally administered liver extract may be brilliant. Moreover, partial failure with the use of parenterally administered liver extract in the hands of others have been turned into success by the use of larger dosage and through greater persistence.¹¹⁸ The intravenous route in such patients has undoubted advantages for the daily administration of the extract derived from as much as 100 Gm. of liver, which may initially be necessary. The accessory value of iron in the relief of the anemia has been pointed out. The tabulated evidence is largely confined to the hematopoietic results, since it is not possible to present the evidence of improvement of the lingual and intestinal symptoms in a similar quantitative manner. In no type of disease are the results of adequate treatment so gratifying and so uniformly successful as in those conditions now recognized as related directly or indirectly to defects of the diet or its subsequent utilization by the patient. A share in such improvement is possible, in our opinion, for practically all sufferers from sprue provided therapy with liver extract is adequate.

CONCLUSIONS

The following morphologic and physiologic observations indicate that sprue is fundamentally a deficiency disease closely related to addisonian pernicious anemia.

MORPHOLOGIC OBSERVATIONS

1. Involvement of the tongue and alimentary tract, the blood and (rarely) the nervous system was observed in sprue, which thus selects the same systems of the body as does pernicious anemia. Although the characteristic frequency and intensity of the manifestations in these systems are typically different in the two diseases, the condition in certain patients with sprue was found to be indistinguishable clinically from that in patients with pernicious anemia.

2. The macrocytic anemia of sprue closely resembled that of pernicious anemia.

3. The megaloblastic proliferation of the normally active bone marrow, found in patients with sprue and macrocytic anemia, resembled closely that of pernicious anemia.

PHYSIOLOGIC OBSERVATIONS

1. The manifestations of the tongue and alimentary tract as well as the macrocytic anemia of sprue were invariably benefited by adequate doses of a liver extract given by parenteral injection and known to be effective in pernicious anemia.

2. Sources of the extrinsic factor, hematopoietically active in persons with pernicious anemia only after contact with normal human gastric juice, were effective alone in certain patients with sprue. In other patients the extrinsic factor was effective on the lingual symptoms or on the macrocytic anemia of sprue only when administered with normal human gastric juice. The dietary histories of many patients with sprue suggested a deficiency of certain sources of the extrinsic factor, such as meat, eggs and whole cereals.

3. The usual absence of the intrinsic factor from the gastric contents of patients with pernicious anemia was paralleled in certain patients with sprue. In other patients with sprue the intrinsic factor was present in the gastric contents.

4. Liver extracts administered orally, as in certain patients with pernicious anemia, were relatively ineffective in many patients with sprue, but on parenteral administration they favorably affected the formation of blood.

5. The liver of a patient who died of sprue and macrocytic anemia, like that of patients with pernicious anemia in relapse, was found to contain no detectable amount of liver extract.

6. As in certain patients with pernicious anemia, an additional hematopoietic response was produced by the administration of iron.

GENERAL CONCLUSIONS

It is believed, therefore, that in sprue, as in pernicious anemia, there is involved the failure of a reaction between an extrinsic factor in the diet, associated in several substances with vitamin B₂ (G), and an intrinsic factor, present in the gastric contents of the normal person. In addition, difficulty with the absorption of substances from the intestinal tract resulting from this hematopoietic reaction is probably involved in certain instances of both diseases. In different patients with sprue the relative importance of these mechanisms is variable. Sprue

with macrocytic anemia thus arises from the variable participation of three defects: of the extrinsic factor, of the intrinsic factor and of absorption. Dietary deficiency of iron, gastric anacidity and intestinal impermeability may also decrease the normal intake of iron.

By means of diets deficient in sources of the extrinsic factor or closely related substances, lingual and gastro-intestinal lesions, macrocytic anemia with megaloblastic bone marrow and degenerative lesions of the spinal cord have been produced in animals. These manifestations can be abolished by means of liver extract or the extrinsic factor. The gastric secretion of pigs fed appropriately defective diets loses its normal content of the intrinsic factor, and the liver becomes deficient in substances normally present and capable of producing increased formation of blood in cases of pernicious anemia. Therefore, the disease picture in animals may reasonably be regarded as analogous to that in patients with sprue. Appropriate dietary defects in man may likewise initiate the physiologic disturbances of the alimentary tract subsequently involved in the production of sprue.

The evidence for the primary etiologic relationship of yeastlike organisms to sprue is not convincingly supported by observations on animals or on man.

The administration of adequate doses of liver extracts effective in pernicious anemia, especially by parenteral injection, is fundamental in the treatment of sprue and its macrocytic anemia. The accessory use of iron is indicated for certain patients.

It is emphasized that adequate doses of liver extract are as important in controlling the manifestations of the alimentary tract as in promoting the formation of blood in cases of sprue.

CLINICAL EXPERIENCE WITH A DERIVATIVE OF SQUILL

JAMES G. CARR, M.D.

AND

JACOB D. MAYER, M.D.

CHICAGO

This study of scillonin includes observations on 104 patients to whom the drug was given for cardiac decompensation. To these 104 patients 119 courses were given. The records for 85 patients are sufficiently complete to be used in compilations; to these patients 97 courses were given. Most of the subjects were observed at the Cook County Hospital, although some were seen at the Evanston, Wesley Memorial and Passavant Memorial Hospitals and the dispensary of Northwestern University Medical School. The drug herein reported on is a derivative of squill supplied to us in the form of tablets of 0.5 and 0.25 mg. The tablets of 0.25 mg. were assayed by Dr. H. B. Van Dyke of the University of Chicago. He reported that each tablet was equal to 1.15 of a cat unit; 1 cat unit was approximately 0.21 mg. This figure is the true average lethal dose to within 19.4 per cent. Each tablet of 0.25 mg. was approximately equivalent to 0.09 mg. of ouabain or to 79 mg. of international standard digitalis powder. Clinically it appeared that over a period of much more than one year the scillonin retained its potency. There was no notable deviation from the average dose necessary for therapeutic effect in any of the lots supplied to us. That the potency is well preserved over a long period will appear from an experience noted later in the paper. The average therapeutic dose was found by us to vary from 8 to 12 mg. (given over a period of four days) for the adult patient of average weight.

The cardiac rate as it is included in these reports was usually that recorded by the senior house physicians. During the period of more intensive treatment at least one daily record of the ventricular rate was made by this physician. These records were checked by one of us with sufficient frequency to satisfy us of their accuracy.

The charts of intake and output of fluid were under the direct supervision of the nurse in charge of the ward. The conditions in a large general hospital are not conducive to accuracy with respect to intake and output of fluid. The efficient service given by the head nurses, especially in the Cook County Hospital, made the charts of output presented here reliable. The standing orders included restriction of fluid to 1,500 cc. daily. In this article the term therapeutic effect

is used. By this term is meant that a dose was followed by definite clinical improvement, including recession of edema, disappearance of dyspnea while the patient was at rest, a fall in the ventricular rate and an increase in the urinary output. In practically all of our cases the initial large dose was followed by a maintenance dose, given for a variable period, of from 0.5 to 0.75 mg. daily.

There were 21 patients with rheumatic cardiac disease, to whom 23 courses of scillonin were given; 6 of these had formerly been patients in the hospital, 1 having a record of fifteen admissions to the Cook County Hospital within six years. Nine had a history of rheumatic cardiac disease over more than fourteen years. Every patient in the group had long been afflicted with cardiac disease. Of 14 patients who showed compensation, 6 were discharged from the hospital within two weeks of the beginning of medication and 11 within one month. There were 20 patients with arteriosclerotic cardiac disease, to whom

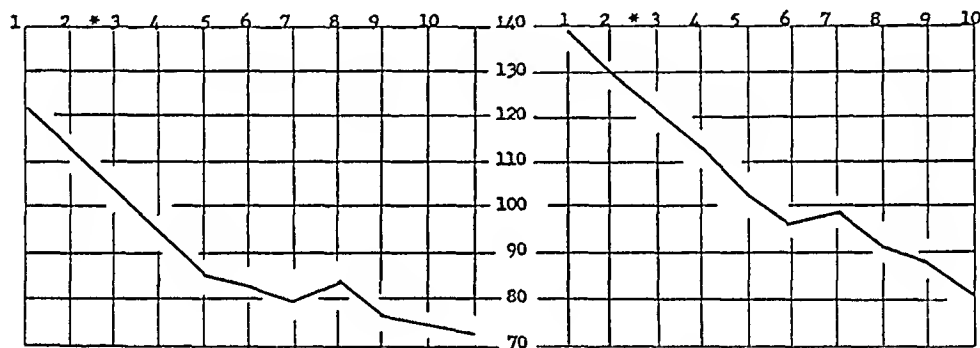


Chart 1.—The ventricular rate in 13 cases of auricular fibrillation with the administration of scillonin begun on the second or third day of hospitalization. The left-hand curve gives the rate of 9 patients who received 9 mg. or more in four days, or an average dose of 10.7 mg. Eight of this group were discharged from the hospital showing compensation within a period of from ten days to two months after scillonin therapy was started. One of the 2 patients who remained in the hospital for more than one month after scillonin therapy was started was allowed to suffer decompensation under our observation (the case is reported in chart 6). The other remained for some weeks to work in the ward. One patient, with severe decompensation, who died with symptoms of acute abdominal distress was shown at autopsy to have had a ruptured bladder. The right-hand curve gives the rate of 4 patients who received less than 9 mg. during the first four days, or an average dose of 7.25 mg. All the patients in this group were discharged from the hospital showing compensation within one month of the beginning of scillonin therapy. The asterisk indicates the approximate time of beginning the administration of scillonin.

26 courses of scillonin were given. Following 23 of the 26 courses the patients were discharged as improved. After 6 of the 26 courses the patients were discharged within two weeks. Six patients were in the hospital for more than a month after the medication was started. Three

patients died while under our care; 2 are known to have reentered the hospital and died shortly after their discharge from our service. To 16 patients with hypertensive cardiac disease 18 courses of the medication were given. Only 1 death occurred in this group. Six of the patients were discharged showing compensation within two weeks of the time the medication was started.

To 21 patients with cardiovascular syphilis 23 courses of the scillonin were given. Eighteen of these patients had aortic insufficiency; in 1 an aneurysm was diagnosed and found anatomically; in the case of 2 the diagnosis between hypertensive and syphilitic cardiac disease could not finally be made. Eleven of these patients died in our ward.

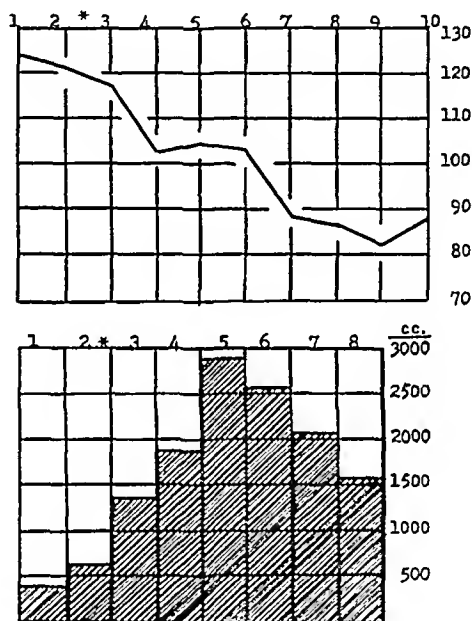


Chart 2.—The ventricular rate of 11 patients with auricular fibrillation and satisfactory records of urinary output. The average dose was 9 mg. in the first four days of therapy; in 5 instances less than 9 mg. was given in the first four days. All the patients in this group were discharged showing compensation, 7 within two weeks of the time scillonin therapy was started.

Another died in a different ward within three weeks of his discharge from our service; he had been discharged from our service showing compensation. The patient with the aneurysm also died within a short time in another ward. Thirteen of the 21 patients died while actually under our observation.

There were 7 patients with one of a miscellaneous group of cardiac diseases: 1 with subacute bacterial endocarditis, 1 with chronic emphysema, 1 with chronic glomerulotubular nephritis and acute endocarditis and 1 with gangrene complicating cardiac failure; only 1 of these 4 (the patient with emphysema) lived. There were 3 other cases in

which an etiologic diagnosis could not be made; these patients were all discharged showing compensation.

Satisfactory records of 14 courses of digitalis previously given to 11 patients in our series were found. For these 11 patients the average length of stay in the hospital under scillonin therapy was nineteen and three-tenths days; for the same patients through 14 courses of digitalis therapy the average duration of the stay in the hospital was eighteen and nine-tenths days. In seven of the fourteen courses of digitalis therapy the maximum therapeutic dosage was given.

One notable feature of the effect of scillonin is the long duration of its effect; marked slowing of the ventricular rate or bigeminal pulse

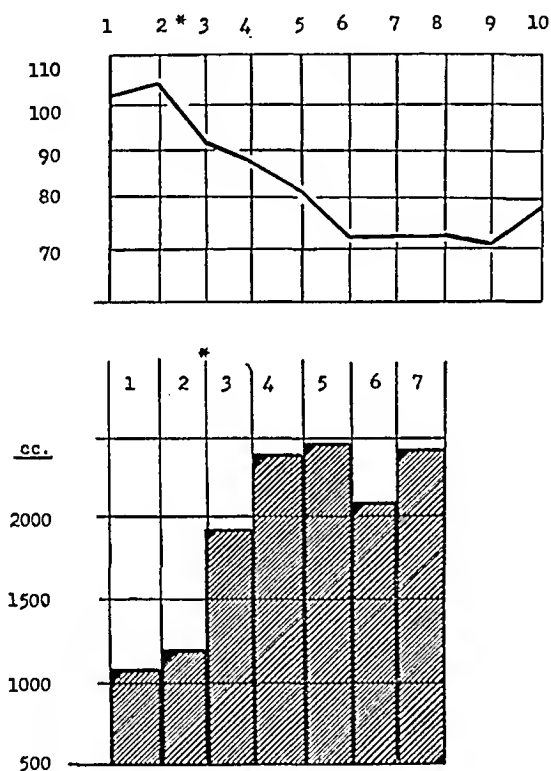


Chart 3.—Composite curves of the ventricular rate and urinary output of 17 patients for whom there was adequate control of the fluid output. Scillonin therapy was started on the third day of hospitalization. The average total dose for the first four days of administration was 8.8 mg. Two of the 17 died; both had cardiovascular syphilis. The other 15 were discharged showing compensation, 6 within two weeks and 7 in from eighteen to thirty days after scillonin therapy was started. One patient was not discharged until seven weeks after medication was started. Another showed compensation twelve days after scillonin therapy was started but remained in the hospital four months to work.

appeared in several instances several days after the medication had been stopped. In 1 case the ventricular rate, 64 when the medication was stopped, was 58 one week later. Another patient had a rate of 50 when medication was stopped; after five days the rate was 56. Bradycardia

developed in 1 patient, with a ventricular rate of 48 after 30 mg. of scillonin had been given in twenty-seven days; nine days thereafter the rate was 44, and on the twelfth day, 54. One patient with nausea and vomiting had a rate of 80 on the day the intoxication appeared. Although no more scillonin was given, the rate was 64 after four days and 60 after six days. Another patient with nausea had a rate of 60 when the scillonin therapy was stopped; eight days later the rate was 50. One patient with a ventricular rate of 48 showed occasional

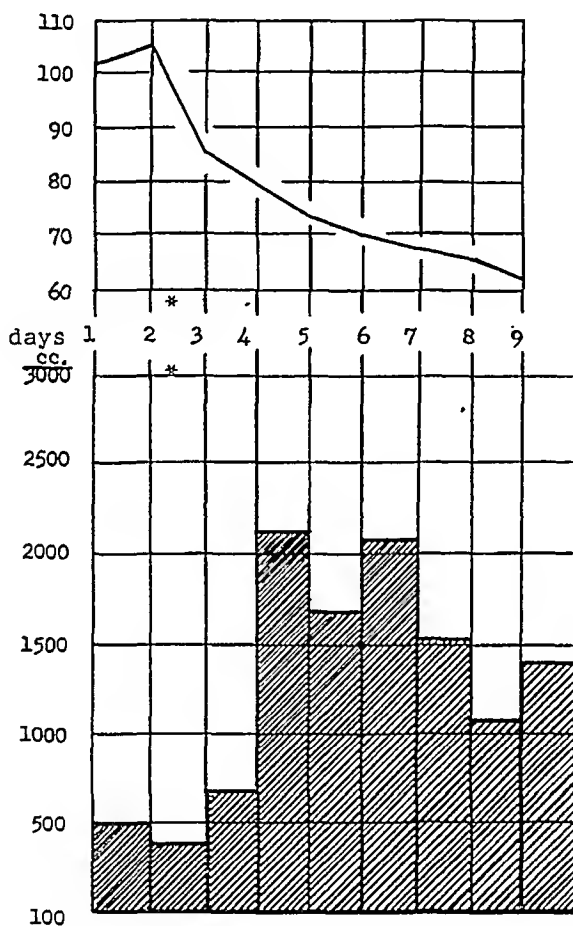


Chart 4.—Composites of the ventricular rate and urinary output of 9 patients to whom the estimated therapeutic dose was given in a short period. Two of these patients received 10 mg. within two days, 2 received 9 mg. within two days, and 1 received 10 mg. within one day, 1 received 12 mg. within three days and the other 3 received 11 mg. within three days. The chart of the urinary output is not satisfactory as it is made up of only six of the nine records. In 6 cases the therapeutic dose was followed by the daily administration of at least 1 mg. for from two to six days. In 2, cardiac irregularities developed: in 1 bigeminal pulse, and in the other, trigeminal pulse. In 1 patient the ventricular rate fell to 56 after 15 mg. of scillonin had been administered in 6 days. In 1 patient to whom 11 mg. was administered in three days auricular fibrillation developed with a ventricular rate of from 30 to 40 the day after the course of scillonin was completed. The group includes only 1 case of established auricular fibrillation.

periods of bigeminal pulse for two weeks after administration of the drug was discontinued. In another case the ventricular rate was 64 when medication was stopped; five days later the rate was 56. In another instance bigeminal pulse persisted for seven days after the scillonin therapy was discontinued.

In this series there were 29 instances in which the pulse (ventricular rate) fell to 60 or below in the course of the treatment, without cardiac irregularity. In one instance the bradycardia occurred in conjunction with an arrhythmia which was not identified. In 12 cases bigeminal pulse appeared. In 1 case trigeminal pulse was found. One patient had paroxysmal tachycardia (the nature of which was not determined) after 31.5 mg. of scillonin had been taken in twenty-three days. Auricular fibrillation developed in 3 patients in the course of the therapy with squill. The first instance of the onset of auricular fibrillation occurred in a man of 28 with rheumatic cardiac disease; the

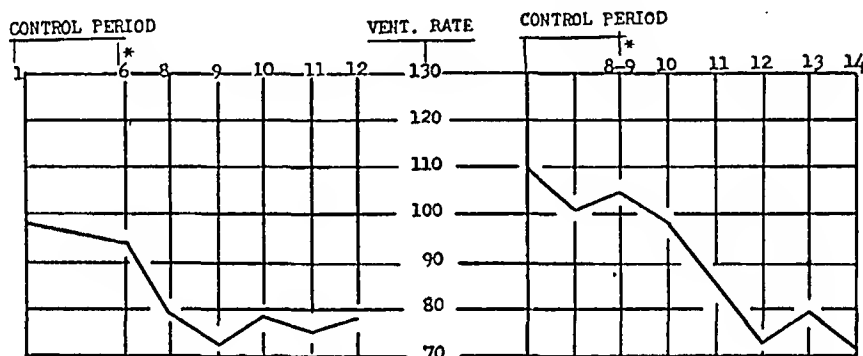


Chart 5.—Composites of the ventricular rate in 15 patients. The left-hand curve gives the rate of 9 patients. The control period was for five days, the maximum dose within four days was 14 mg., and the average dose within four days was 10.6 mg. In 2 of the earlier cases 8 mg. was given in the first four days, and 1 patient, a small Filipino of 19, received only 6 mg. in four days. The right-hand curve gives the rate of 6 patients. The control period was for eight or nine days, the maximum dose within four days was 14 mg., and the average dose within four days was 10.3 mg. In 1 case only 8 mg. was given within the first four days of treatment. Twelve of the 15 patients were discharged showing compensation after periods of from one to four weeks following the beginning of scillonin medication. One patient showed compensation promptly but was in the hospital for ten weeks because of complicating diabetes. One patient with low grade acute endocarditis and congestive failure was discharged showing compensation after twelve weeks. One patient with a cerebral hemorrhage, to whom scillonin was given merely to control the ventricular rate, died.

administration of scillonin was continued in daily doses of 1 mg. The fibrillation persisted through four days. The second case was that of a woman of 46 with cardiovascular syphilis and hypertension, in whom fibrillation developed after 36 mg. had been taken in twenty-six days.

The administration of scillonin was discontinued, and within five days the normal mechanism was reestablished. In the third case 11 mg. of scillonin was given within three days, following which the fibrillation appeared. The normal mechanism reappeared after five days.

Nausea was present in 12 patients. In 2 gastric distress and nausea were present at the time of admission and disappeared as the scillonin produced its favorable effect on the circulation. There were therefore 10 cases in which nausea was attributable to the scillonin. In 1 instance, coincidental with the appearance of bigeminal pulse, the patient stated that he could "easily be nauseated." In 3 instances cardiac irregularity or pronounced bradycardia preceded the nausea; in 1 instance bradycardia and in another bigeminal pulse were discovered when the nausea

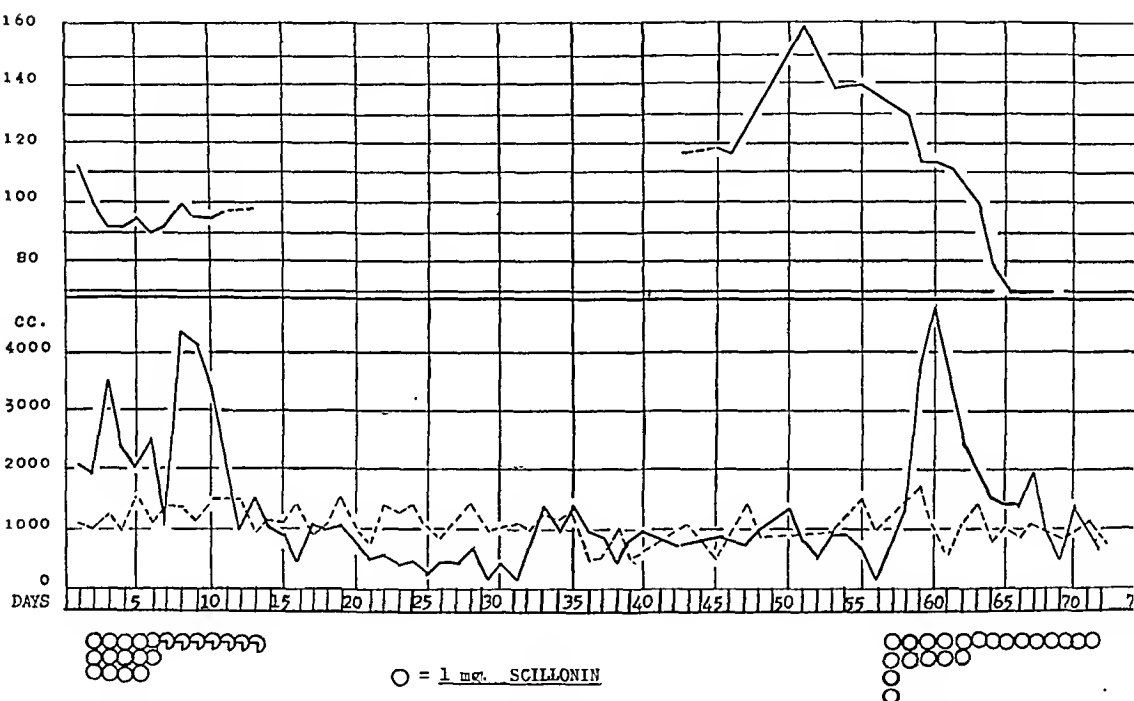


Chart 6.—The upper curve represents the ventricular rate, the lower solid curve the urinary output and the broken curve the fluid intake of 1 patient (case 44). Scillonin therapy was started on the second day of hospitalization and was discontinued after thirteen days. No scillonin or other drug of the digitalis group was given thereafter until the fifty-seventh day. Meanwhile, after thirty-two days without medication other than an occasional dose of magnesium sulphate the patient showed signs of decompensation. He was allowed to be up and about the ward for six days. By this time he showed marked decompensation, with the ventricular rate 160. He was put to bed for six days with no medication except an occasional dose of morphine. Scillonin therapy was recommenced on the fifty-seventh day.

was first reported, and twice the cardiac irregularity followed closely on the complaint of nausea. Twice nausea occurred alone. Nausea in the course of scillonin medication is not the relatively mild early sign

of intoxication with which one is familiar in the course of digitalis therapy. The nausea of scillonin intoxication signifies a marked degree of intoxication and calls for the immediate discontinuance of the drug.

In 9 of the 29 cases in which marked bradycardia occurred the slow rate came on after rather small doses of scillonin were given; in each case less than 10 mg. was administered in periods ranging from two to seven days, and the average dose was 8.25 mg. In 5 of these 9 cases digitalis had probably been given within a short time prior to admission to the hospital; in 1 a course of scillonin had been discontinued three weeks earlier. Of the 13 patients with bigeminal pulse, in only 3 did the rhythm develop when less than 10 mg. of scillonin had been taken, and

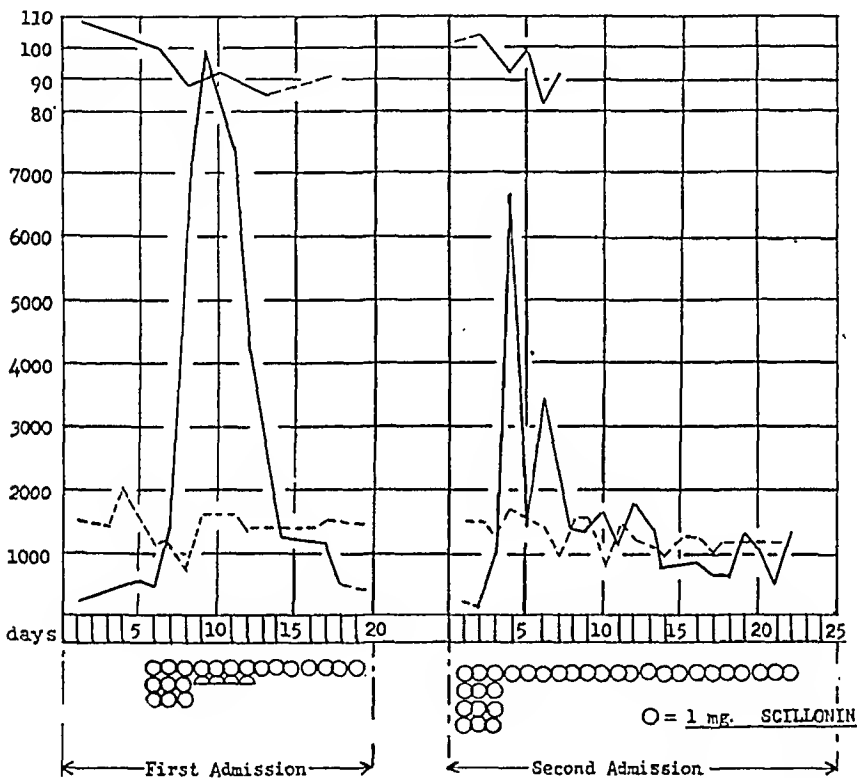


Chart 7.—The upper curve represents the ventricular rate, the lower solid curve the urinary output and the broken curve the fluid intake of 1 patient (case 48). The record of the first admission shows the result of scillonin medication started on the sixth day of hospitalization. The record of the second admission, six weeks after the first, shows the result of scillonin medication started on the first day.

2 of these 3 had taken digitalis within a period of a week or more. Of the patients with bradycardia, 8 had taken squill for ten days or more. The duration of medication varied from ten to twenty-eight days, and the total dosage, from 12 to 33 mg. An average for each patient of 20.7 mg. was taken during fifteen and seven-tenths days. Ten patients in whom bigeminal pulse developed received from 13 to 30 mg. in periods varying from nine to twenty-three days, an average of

18.5 mg. within nine and eight-tenths days. Nine patients who became nauseated received from 7 to 24 mg. over periods varying from three to twenty-one days, an average of 17 mg. in ten and six-tenths days. It appears that the total dose likely to produce nausea is about the same as that which produces cardiac irregularity, although in these small groups nausea appeared following a smaller average daily dose than was necessary to produce cardiac irregularity.

There were 2 deaths attributable to the scillonin. In spite of emphasis on the importance of discontinuing the administration of scillonin if any signs of digitalis intoxication appeared, a patient was allowed to receive 5 mg. through two and one-half days after nausea developed. He died two days after the drug was withdrawn. He did not have a cardiac rate below 68, nor did he show cardiac irregularity. He presented a late stage of cardiovascular syphilis with marked anemia. In another ward than our own a patient with long-standing rheumatic disease, advanced decompensation and digitalis intoxication was treated for five days with rest, promoted by an occasional dose of morphine. Scillonin therapy was then started, 3 mg. administered daily for two days, followed by 2 mg. every day for three days. On the third day of this routine the pulse was "irregular"; on the fourth day nausea was present, and on the fifth day the patient died. It cannot be too clearly stated that scillonin manifests all the therapeutic and toxic effects of digitalis. It produces the usual effects of digitalis, because of which it is valuable in the treatment of cardiac decompensation. It is not to be used as a substitute for digitalis in the presence of digitalis intoxication.

SUMMARY

1. Scillonin, a derivative of squill, will produce the usual effects of digitalis in the treatment of cardiac decompensation. Essentially the same therapeutic and toxic results are obtained as occur with the use of digitalis.

2. In our experience cardiac irregularities are likely to be the first signs of dangerous intoxication. Nausea does occur and may precede the appearance of cardiac irregularities. The nausea of scillonin intoxication is significant in that it appears to signify a more advanced grade of intoxication than that associated with the nausea of digitalis. Nausea and cardiac irregularities occurring in the course of treatment with scillonin are symptoms which call for the immediate discontinuance of administration of the drug.

3. Slowing of the cardiac rate to 60 or below is frequent with the successful use of scillonin. The onset of a rate as low as 60 is significant of the full therapeutic dose and calls for discontinuance of scillonin medication temporarily.

4. A dose of from 8 to 12 mg. of scillonin of standard potency as now provided, depending on the weight of the patient, may be given within four days to patients who are known to have taken no drug of the digitalis group within two weeks. If a prior course of scillonin or of some other drug of the digitalis group has been used with full therapeutic effect, the maximum dosage of scillonin should not be repeated within a month. Under these circumstances small doses may be given daily until the effect appears. The maintenance dose of scillonin is approximately 0.5 mg. per day, but it must be adapted to the needs and response of the individual patient. In a few cases in private practice the patient has been kept on a small daily ration for three years or more. For small patients the daily maintenance dose is as low as 0.33 mg.

5. Scillonin therapy is of advantage to certain persons who take digitalis with difficulty because of gastric distress early in the course of medication. Scillonin may be recommended for these patients. It is not a substitute for digitalis in the presence of frank digitalis intoxication. When digitalis has been given recently only small doses of scillonin are permissible. The desired effect may be achieved by daily doses somewhat larger than the maintenance dose.

6. Scillonin retains its potency over a long period. A supply in our possession for about seventeen months proved as effective at the end of that time as the lots recently assayed.

EFFECT OF DIGITALIS ON THE CARDIAC OUTPUT OF PERSONS WITH CONGESTIVE HEART FAILURE

BEN FRIEDMAN, M.D.

NEW YORK

AND

GURNEY CLARK, M.D.

HARRY RESNIK JR., M.D.

AND

T. R. HARRISON, M.D.

NASHVILLE, TENN.

The observations to be presented in this report constitute a part of a general study of the functional alterations concerned in the production of the clinical picture of congestive heart failure. One method of obtaining information concerning such alterations is to inquire into the mechanism whereby therapeutic measures produce clinical improvement. It is now generally recognized not only that digitalis is the sovereign remedy for heart failure in patients with auricular fibrillation but that this drug is often beneficial to persons with regular rhythm. In the former group of patients clinical improvement may be ascribed to the dramatic slowing of the heart, but in the latter group changes in the cardiac rate are usually slight, and an adequate explanation for the benefits from digitalis has yet to be offered. According to some investigators, the effects are dependent on an increase in the output of the heart per minute; other authors have expressed the opinion that the drug has the reverse effect.

In the isolated heart of the frog digitalis causes an increase in the strength of the contraction, so that the heart empties itself more completely. Similar effects may be noted in a perfused mammalian heart. The output per beat is therefore usually increased, and the output per minute may or may not be increased, according to whether the greater contraction does or does not predominate over the diminished rate of the heart.¹

Various results have been arrived at by workers who have utilized the heart-lung preparation to study the effects of digitalis. Bijelsma and

From the Department of Medicine, Vanderbilt University School of Medicine.

1. Cushny, A. R.: Textbook of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1928.

Roessingh² observed that strophanthin diminished the size of the heart but did not change its output, and similar observations were reported by Bodo³ with digitalis. Plant⁴ studied hearts which had been poisoned by phosphorus and noted that strophanthin caused a temporary increase in the amplitude of contraction. Cohn and Steele⁵ administered digitalis to hearts which were failing, as shown by a rise in the auricular pressure and a decrease in the output. The drug caused a temporary reversal of these effects, the output increasing and the auricular pressure diminishing.

On the other hand, digitalis has been shown to diminish the output of the heart of normal dogs (Harrison and Leonard⁶; Cohn and Stewart⁷; Dock and Tainter⁸) and of normal human beings (Burwell, Neighbors and Regen⁹; Stewart and Cohn¹⁰).

Concerning the effect of the drug on the cardiac output of patients with cardiac disease, there is considerable doubt. Increase in the output

2. Bijelsma, U. G., and Roessingh, M. J.: Die Dynamik des Säugetierherzens unter dem Einfluss von Stoffen der Digitalisgruppe, *Arch. f. exper. Path. u. Pharmacol.* **94**:235, 1922.

3. Bodo, R.: The Effect of the "Heart-Tonics" and Other Drugs upon the Heart-Tone and Coronary Circulation, *J. Physiol.* **64**:365, 1928.

4. Plant, O. H.: A Note on the Efficiency of the Knowlton-Starling Isolated Heart-Lung Preparation for Testing the Cardiac Action of Drugs, *J. Pharmacol. & Exper. Therap.* **5**:603, 1913-1914.

5. Cohn, A. E., and Steele, J. M.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: I. The Effect on the Output of the Dog's Heart in Heart-Lung Preparations, *J. Clin. Investigation* **11**:871, 1932.

6. Harrison, T. R., and Leonard, B. W.: The Effect of Digitalis on the Cardiac Output of Dogs and Its Bearing on the Action of the Drug in Heart Disease, *J. Clin. Investigation* **3**:1, 1926.

7. Cohn, A. E., and Stewart, H. J.: The Relation Between the Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Normal Dogs, *J. Clin. Investigation* **6**:53, 1928; The Relation Between the Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Dogs in Which the Heart Is Enlarged, *ibid.* **6**:79, 1928.

8. Dock, W., and Tainter, J. L.: The Circulatory Changes After Full Therapeutic Doses of Digitalis, with a Critical Discussion of Views on the Cardiac Output, *J. Clin. Investigation* **8**:467, 1929.

9. Burwell, C. S.; Neighbors, D. W., and Regen, E. M.: The Effect of Digitalis on the Output of the Heart in Normal Man, *J. Clin. Investigation* **5**:125, 1927.

10. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: Effect on the Output of Hearts of Dogs Subject to Artificial Auricular Fibrillation, *J. Clin. Investigation* **11**:897, 1932; Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart; the Effect on the Output in Normal Human Hearts; the Effect on the Output of Hearts on Heart Failure with Congestion, in Human Beings, *ibid.* **11**:917, 1932.

was reported by Ringer and Altschule¹¹ and likewise by Lauter and Baumann,¹² who used the method employing ethyl iodide. Eppinger, von Papp and Schwarz¹³ and Schwarz,¹⁴ employing a modification of an indirect Fick method employing oxygen, reported that digitalis caused a decrease in the cardiac output. Ewig and Hinsberg,¹⁵ with the method employing carbon dioxide, observed no change in the cardiac output following the administration of digitalis; and Kininmonth,¹⁶ with the ethyl iodide procedure, found that clinical improvement following the administration of digitalis might be associated with an increase, with a decrease or with no change in the minute output of the heart.

Recent studies of Grollman¹⁷ have cast doubt on the validity of these various methods, even in normal subjects, and their applicability to persons with cardiac disease is therefore dubious. On the other hand, Grollman has presented convincing evidence of the reliability in normal subjects of his method employing acetylene. In view of this evidence, the observations of Stewart and Cohn,¹⁰ who studied the effect of digitalis in persons with cardiac disease by means of the acetylene method are entitled to special consideration. These authors reported a consistent increase in the output of the heart per minute following the administration of digitalis to six of seven subjects suffering from a failing heart. After their paper had been published, a critical study of the reliability of methods for determining the cardiac output of patients with cardiac disease was made by Grollman, Friedman, Clark and Harrison.¹⁸ They found that it is impossible to obtain accurate results in certain patients with cardiac failure but that in other patients reliable data can be procured provided a minor modification is introduced into

11. Ringer, M., and Altschule, M.: Studies on the Circulation: II. Cardiac Output in Diseases of the Heart and Under the Influence of Digitalis Therapy, *Am. Heart J.* **5**:305, 1929.

12. Lauter, S., and Baumann, H.: Zur Theorie der Herzinsuffizienz und der Digitaliswirkung, *Klin. Wchnschr.* **8**:263, 1929.

13. Eppinger, H.; von Papp, L., and Schwarz, H.: Ueber das Asthma cardiale, Berlin, Julius Springer, 1924.

14. Schwarz, H.: Zur Theorie der Herzinsuffizienz und der Digitaliswirkung: Kritische Bemerkungen zur Arbeit von Lauter und Baumann, *Klin. Wchnschr.* **8**:599, 1929.

15. Ewig, W., and Hinsberg, K.: Neue Methode zur Bestimmung des Herzminutenvolumens, *Ztschr. f. klin. Med.* **115**:677, 1931.

16. Kininmonth, J. G.: The Circulation Rate in Some Pathological States, with Observations on the Effect of Digitalis, *Quart. J. Med.* **21**:279, 1928.

17. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

18. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, *J. Clin. Investigation* **12**:751, 1933.

the technic and certain criteria are fulfilled. In the absence of such controls results in error by as much as 50 per cent were sometimes encountered, and seriously fallacious data were frequently obtained. The observations of Grollman and his colleagues cast doubt on the validity of the conclusions drawn by Stewart and Cohn, and therefore we have felt that the problem should be restudied, with the newer technic, which not only is free from certain theoretical errors but has been checked against another more laborious method based on an entirely different principle.¹⁹

METHOD

The subjects studied were adults with various degrees of congestive heart failure dependent on the usual etiologic factors. Since it was often impossible to obtain accurate results in patients with marked decompensation, the subjects chosen usually presented mild or moderate congestive phenomena. They were trained to the rebreathing procedure for one or more days prior to the beginning of the observations. Several of the subjects had been examined previously and were accustomed to respiratory gymnastics.

The plan of procedure was as follows: The patient, in the basal condition, was brought to the laboratory in a wheel-chair. The consumption of oxygen was determined in duplicate by analysis of the expired air with the Haldane apparatus. The technic used for measuring the arteriovenous oxygen difference was that described in previous papers.²⁰ Two rebreathings were usually done, the samples of gas being obtained at approximately twenty-two, twenty-six and thirty seconds in the first and two seconds later in the second. The time of sampling was varied somewhat according to previous knowledge of the subject's ability to secure a mixture in the lung-bag system and of the time at which recirculation occurred. When the subject breathed poorly or failed to empty the bag completely, the observation was discarded.

During the control period, the patients were kept at rest in bed and ordinarily received no therapy other than sedatives and limitation of food and fluids. In a few instances diuretics were given prior to the administration of digitalis. Following one or more successful determinations of the cardiac output, digitalis was administered, the usual dose being 1.5 Gm. of a standardized powdered leaf on the first day, from 0.3 to 0.6 Gm. of the standardized powdered leaf on the second day and a daily maintenance dose of 0.2 Gm. thereafter.

The patients studied were divided into three groups on the basis of their clinical response to digitalis. Definite improvement was considered to have occurred when one or more of the following phenomena appeared during the first three days of administration of digitalis: (1) diuresis, as shown by rapid decrease in the body weight; (2) a rise in the vital capacity of 15 per cent or more, and (3) cessation of paroxysmal dyspnea, which had been persistent prior to the administration of digitalis. A patient was classified as exhibiting questionable improvement when, in addition to his subjective claim that dyspnea was improved,

19. Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXII. A Method for Obtaining "Mixed" Venous Blood by Arterial Puncture, *J. Clin. Investigation* **13**:533, 1934.

20. Grollman, Friedman, Clark and Harrison.¹⁸ Friedman, Clark and Harrison.¹⁹

TABLE 1.—Observations on Patients Showing Definite Improvement After the Administration of Digitalis

Patient	Diagnosis	Date 1933	Dyspnea*	Edema	Weight, Pounds	Vital Capacity, Liters	Heart Rate	Oxygen Consumption per Minute, Cc.	Arterio-venous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Cardiac Output per 100 Cc. of Oxygen Absorbed	Duration of Administration, Days	Total Amount of Digitalis Given, Gm.	Comment
J. E.	Hypertension	2/24	+++	++	138	2.05	88	241	84.6	2.85	1.18	..	0	Paroxysmal dyspnea ceased
		3/3	+++	+	123	2.30	88	184	93.7	2.07	1.33	..	0	
		3/6	++	0	116	2.50	76	192	80.0	2.45	1.25	3	2.1	
		3/7	+	0	115	2.60	73	214	91.6	2.34	1.09	4	2.3	
		3/8	+	0	116	2.60	74	221	85.2	2.59	1.17	5	2.5	
		3/9	+	0	116	2.85	70	169	70.0	2.42	1.43	6	2.7	
		3/10	+	0	115	2.70	66	179	73.8	2.23	1.27	7	2.9	
		3/11	+	0	115	2.70	66	199	85.8	2.32	1.17	8	3.1	
		5/18	+++	0	217	2.75	58	225	66.3	3.39	1.67	..	0	Paroxysmal dyspnea ceased
		5/19	+++	0	216	2.75	61	220	66.4	3.31	1.63	..	0	
		5/20	++	0	214	2.85	61	208	45.4	4.53	2.26	..	1.5	
G. B. S.	Hypertension, auricular fibrillation	5/22	++	0	214	3.40	62	220	75.3	2.92	1.33	3	2.5	
		5/23	+	0	214	3.10	61	206	68.9	2.99	1.45	4	2.8	
		8/9	+++	++	196	1.50	89	319	85.7	3.32	1.17	..	0	Paroxysmal dyspnea ceased
		8/11	+++	++	194	1.70	92	307	90.2	3.40	1.11	..	0	
		8/13	++	++	190	1.80	84	304	76.4	3.98	1.31	1	1.5	
M. O.	Hypertension, auricular fibrillation	8/14	+	++	192	1.93	79	295	98.4	3.30	1.02	2	2.1	
		8/16	+	++	193	1.95	82	305	74.0	4.12	1.35	4	2.7	
		8/7	+++	+	230	3.10	75	332	89.5	4.23	1.12	..	0	Paroxysmal dyspnea ceased
		8/8	+++	++	238	3.00	69	362	82.6	4.33	1.21	..	0	
		8/9	++	++	237	3.13	75	378	90.2	4.13	1.11	1	1.5	
I. M.	Mitral stenosis, auricular fibrillation	8/10	+++	+	236	3.50	70	407	104.5	3.89	0.96	2	2.1	
		8/11	++	0	234	3.60	70	378	103.1	3.63	0.97	3	2.5	
		8/12	+	0	235	3.40	72	403	103.0	3.80	0.94	4	2.9	
		12/12	+++	+	126	2.20	128	245	101.9	2.40†	0.98	..	0	Paroxysmal dyspnea ceased
		12/14	+	0	122	2.60	84	216	96.6	2.37	1.03	1	1.7	
A. E.	Syphilitic myocarditis	12/16	+	0	121	2.80	74	206	83.7	2.40	1.17	3	2.1	
		2/20	+++	++	165	1.85	90	254	88.1	2.89	1.13	..	0	Paroxysmal dyspnea ceased
		2/21	+++	++	165	1.95	91	247	85.0	2.91	1.18	..	0	
		2/22	+++	++	165	1.90	85	247	68.9	3.59	1.45	1	1.5	
		2/23	+++	++	161	2.05	74	243	71.1	3.43	1.41	2	2.3	
O. M.	Syphilitic aortic insufficiency	2/27	++	+	145	2.65	70	236	79.6	2.96	1.26	6	3.12	
		2/28	+	+	143	2.80	68	200	67.2	2.98	1.49	7	3.3	
		3/2	+	0	138	2.90	66	232	86.6	2.92	1.15	9	3.5	
		3/6	+	0	138	3.00	66	252	71.5	3.52	1.40	13	4.3	
		3/7	+	0	138	3.00	66	278	78.0	3.52	1.28	14	4.5	
A. M.	Syphilitic aortic insufficiency	3/8	+	0	137	3.00	72	247	77.8	3.18	1.28	15	4.7	
		7/26	+++	++	144	2.10	84	265	94.9	2.16	1.05	..	0	Paroxysmal dyspnea ceased
		7/27	+++	++	144	1.75	80	196	98.8	1.93	1.01	..	0	
		7/28	++	++	143	2.35	66	211	90.8	2.32	1.10	1	1.6	
		7/29	++	++	143	2.10	62	222	77.0	2.88	1.30	2	1.9	
A. M.	Syphilitic aortic insufficiency	8/1	+	0	131	2.40	62	214	97.5	2.19	1.03	5	2.7	
		8/24	+++	++	163	2.50	76	272	112.6	2.42	0.89	..	0	Received salyrgan
		8/25	+++	++	161	2.60	76	290	113.8	2.55	0.88	..	0	
		8/26	++	+	151	2.90	78	278	117.9	2.36	0.85	..	0	
		8/27	+	+	147	3.15	71	254	105.4	2.41	0.95	1	0.6	
		8/28	+	0	143	3.15	73	251	97.9	2.68	1.02	2	1.2	
		8/29	+	0	143	3.40	66	230	119.2	1.93	0.84	3	1.8	
		8/30	+	0	144	3.20	69	226	118.3	2.02	0.85	4	2.4	
		8/31	+	0	144	3.20	64	221	106.6	2.23	0.99	5	2.6	
		9/1	+	0	143	3.25	64	224	105.4	2.12	0.95	6	2.8	

* In this and the following tables the symbols +, ++, +++ refer, respectively, to dyspnea on moderate exertion, dyspnea on slight exertion, dyspnea on exertion plus slight dyspnea while at rest and ++++ refer, respectively, to dyspnea on exertion plus moderate dyspnea while at rest.

† The cardiac output of this patient was determined by the venous plateau method.

there occurred either a rise in vital capacity of less than 15 per cent or a cessation of previously intermittent paroxysmal dyspnea. Subjects who showed neither well defined subjective nor well defined objective changes after the administration of digitalis were classified as unimproved.

In analysis of the data, changes of less than 10 per cent in the cardiac output and arteriovenous oxygen difference were not considered significant, because the analytic procedures involve a possible error of this general magnitude.

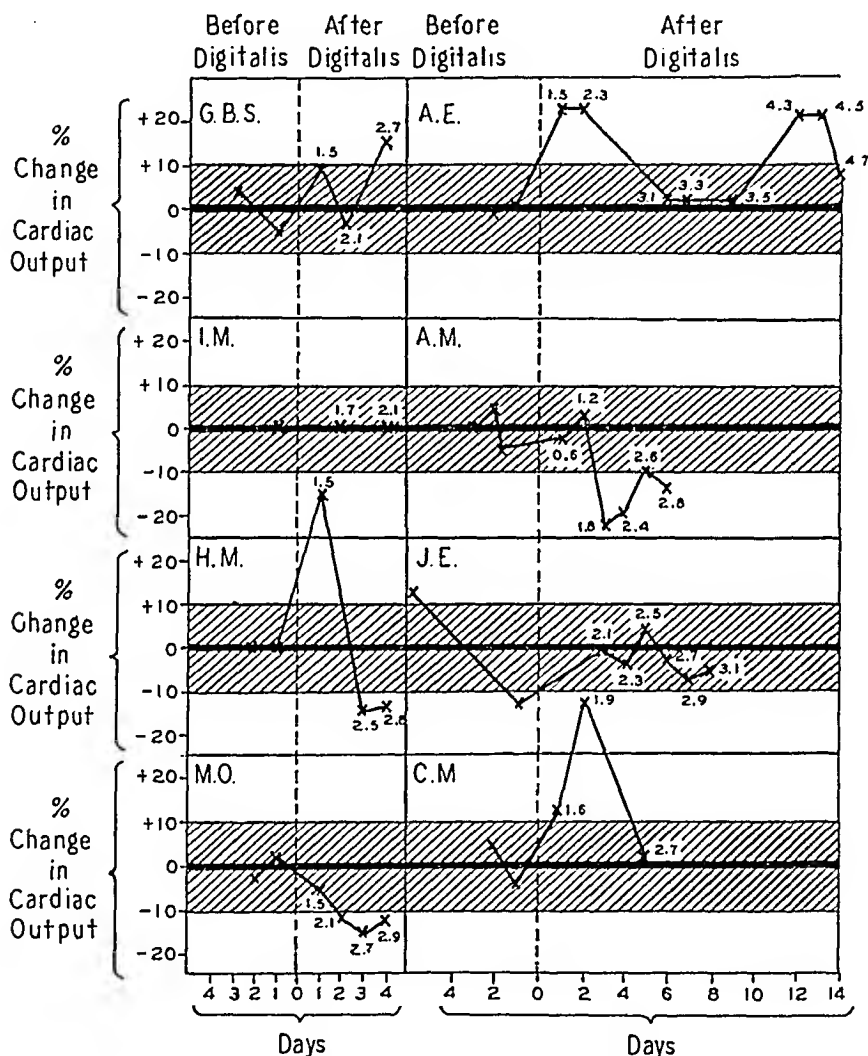


Chart 1.—The data are plotted for the subjects who exhibited definite improvement following the administration of digitalis. The central bar represents the average value for the cardiac output before the administration of digitalis. Changes within 10 per cent of this (represented by the shaded areas) are not considered significant; the numbers refer to the total amount (in grams) of digitalis received at the time of the observation.

RESULTS

According to Grollman,¹⁷ who investigated a large group of healthy subjects, the normal cardiac output is 2.2 ± 0.3 liters per square meter of body surface. Prior to the administration of digitalis the range of values in our patients was between 1.34 and 2.09 liters per square meter,

the values being below Grollman's normal range in thirty-five of forty-two determinations on twenty-two subjects. Per hundred cubic centimeters of oxygen absorbed the cardiac output of the patients before receiving digitalis was from 0.85 to 1.52 liters, being less than 1.4 liters, the lower normal limit in thirty-six of forty-two observations. These data are in agreement with our previous report²¹ that the cardiac output is usually subnormal but may be within normal limits in persons with congestive heart failure.

The data on the eight patients who exhibited definite improvement following the administration of digitalis are shown in table 1 and chart 1. Following the administration of the drug, dyspnea became less marked or disappeared in all the patients, and paroxysmal dyspnea ceased in the six patients who showed it prior to administration of the drug. Seven of the subjects had edema of some degree, and in six it disappeared. The vital capacity of each subject increased. One of the patients (I. M.) had auricular fibrillation with a rapid ventricular rate, which diminished to normal following the administration of the drug. Two patients with fibrillation with a slower ventricular rate had less striking changes in the heart rate. The heart rate became slower in four of the five patients with normal rhythm. The consumption of oxygen per minute was definitely less after the administration of digitalis in two subjects (I. M., A. M.) and was unchanged or showed variations in the others.

An increase in the cardiac output was evident at four of eight examinations in one of the eight subjects (A. E.). Two patients (A. M.; M. O.) showed a slight decrease in the output of the heart per minute at two or three examinations. In one patient (I. M.), who showed marked improvement following digitalis therapy, no change in the cardiac output was revealed at either of two examinations. The remaining four subjects exhibited inconstant fluctuations.

The arteriovenous oxygen difference, which is an inverse measure of the cardiac output in proportion to metabolism, likewise failed to undergo constant change. A significant diminution in the arteriovenous difference occurred in two subjects (I. M.; A. E.); a significant increase occurred in one patient (M. O.), and fluctuations in either direction were noted in the other subjects.

Eleven patients were classified as exhibiting questionable (i.e., chiefly subjective) improvement following digitalis therapy. In these persons fluctuations in the cardiac output occurred (table 2, chart 2).

21. Harrison, T. R.; Friedman, Ben; Clark, Gurney, and Resnik, Harry: The Cardiac Output in Relation to Cardiac Failure, *Arch. Int. Med.* **54**:239 (Aug.) 1934.

TABLE 2.—Observations on Patients Showing Questionable Improvement After the Administration of Digitalis

Patient	Diagnosis	Date	Dyspnea	Edema	Weight, Pounds	Vital Capacity, Liters	Heart Rate	Oxygen Consumption per Minute, Cc.	Arterio-venous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Cardiac Output, Liters per 100 Cc. of Oxygen Absorbed	Cardiac Output per Square Meter	Duration of Administration, Days	Total Amount of Digitalis Given, Gm.	Comment
P. F.	Hypertension	3/30	++	0	176	2.30	84	249	75.6	3.30	1.32	1.78	..	0	Paroxysmal dyspnea ceased
		3/31	++	0	175	2.40	77	245	79.0	3.11	1.27	1.68	..	0	
		4/4	++	0	174	2.35	68	237	60.8	3.90	1.67	2.11	4	2.7	
		4/5	++	0	173	2.50	76	241	80.6	2.98	1.24	1.61	5	3.0	
		4/7	++	0	173	2.40	62	236	59.6	3.95	1.68	2.14	7	3.2	
L. M.	Hypertension	4/8	++	0	174	2.50	64	222	65.5	3.39	1.53	1.83	8	3.4	
		3/21	++	++	163	2.20	96	247	99.9	2.47	1.01	1.36	..	0	Paroxysmal dyspnea ceased
		3/23	++	++	163	2.20	94	254	81.1	3.12	1.23	1.71	1	1.5	
		3/24	++	0	160	2.45	90	273	89.7	3.07	1.12	1.69	2	1.9	
		3/25	++	0	160	2.35	85	264	94.2	2.81	1.06	1.54	3	2.2	
J. M.	Hypertension	3/27	++	0	150	2.50	86	262	94.8	2.76	1.06	1.52	5	2.6	
		11/4	++	0	148	3.00	80	219	82.0	2.67*	1.22	1.48	..	0	Paroxysmal dyspnea ceased
		11/5	++	0	144	2.90	77	235	83.8	2.80	1.19	1.56	..	0	
		11/7	++	0	146	2.90	58	233	72.7	3.20	1.38	1.78	2	2.0	
		11/9	+	0	147	3.15	64	231	70.3	3.28	1.42	1.82	4	2.4	
M. B.	Hypertension	6/12	++	0	...	2.60	60	240	75.8	3.17	1.32	1.71	..	0	
		6/14	++	0	...	2.90	58	242	70.7	3.16	1.30	1.71	1	1.0	
		6/16	++	0	...	2.60	56	247	74.2	3.83	1.35	1.80	3	1.7	
		6/17	++	0	...	2.65	60	263	87.2	3.01	1.15	1.63	4	1.9	
		5/20	++	++	185	2.85	74	308	100.7	3.04	0.99	1.58	0	0	
T. K.	Hypertension, arteriosclerosis, auricular fibrillation	6/3	++	++	183	2.80	59	292	102.6	2.88	0.97	1.50	5	2.2	
		4/26	++	++	125	1.60	76	173	74.7	2.32	1.34	1.60	..	0	
		4/29	++	++	125	1.50	70	208	72.0	2.85	1.39	1.97	..	0	
		5/2	++	++	124	1.65	56	171	71.7	2.39	1.39	1.65	2	2.1	
		5/3	++	++	124	1.70	52	193	75.8	2.55	1.32	1.76	3	2.1	
L. W.	Mitral stenosis	8/2	++	0	119	3.05	68	239	70.5	3.38	1.42	2.09	..	0	
		8/7	++	0	121	3.00	84	224	66.0	3.39	1.32	2.09	..	0	
		8/9	++	0	121	3.00	66	210	66.3	3.17	1.30	1.96	2	2.0	
		8/11	++	0	120	3.30	69	223	78.7	2.82	1.27	1.74	4	2.6	
		8/12	++	0	119	3.10	80	212	83.3	2.55	1.20	1.58	5	2.9	
M. L.	Mitral stenosis, auricular fibrillation	4/27	++	0	126	2.00	83	187	91.1	2.05	1.10	1.36	..	0	
		4/28	++	0	127	2.00	80	182	83.2	2.19	1.20	1.45	..	0	
		4/30	+	0	127	2.30	92	173	96.5	1.79	1.04	1.19	1	1.5	
		5/3	+	0	127	2.20	72	187	96.8	1.93	1.03	1.28	2	2.1	
		5/2	0	0	126	2.20	72	205	103.6	1.98	0.97	1.31	3	2.4	
A. T.	Mitral stenosis	5/4	0	0	127	2.10	80	179	89.4	2.00	1.12	1.32	5	3.0	
		7/22	++	++	96	1.70	82	186	87.5	2.13	1.14	1.70	..	0	
		7/24	++	++	97	1.60	80	235	108.9	2.16	0.92	1.73	..	0	
		7/25	++	++	97	1.80	98	200	106.7	1.88	0.94	1.51	..	0	
		7/26	++	++	95	1.60	82	156	89.1	1.75	1.12	1.40	1	1.2	
Y. D.	Syphilitic aortic insufficiency	7/28	++	++	95	1.65	70	171	75.8	2.25	1.32	1.80	3	1.6	
		7/29	++	++	95	1.75	72	185	100.2	1.85	1.00	1.48	4	1.8	
		6/6	++	0	186	2.55	84	263	105.5	2.38	0.95	1.43	..	0	Paroxysmal dyspnea ceased
		6/7	++	++	136	2.70	75	252	102.2	2.47	0.98	1.48	..	0	
		6/8	++	0	136	2.60	69	239	89.6	2.67	1.12	1.60	1	1.5	
G. M.	Syphilitic myocarditis	6/9	++	0	134	2.50	62	249	98.7	2.52	1.01	1.51	2	2.4	
		6/10	+	0	137	2.55	63	227	94.1	2.41	1.06	1.44	3	2.7	
		9/8	++	++	145	1.90	74	251	78.0	3.21	1.28	1.96	..	0	
		8/11	++	++	135	2.00	80	235	67.0	3.39	1.30	2.07	..	0	
		8/13	++	++	137	2.00	78	241	76.0	3.19	1.32	1.95	..	0	
		9/15	+	0	131	2.20	82	238	89.0	2.68	1.12	1.61	2	1.2	
		9/16	++	0	132	2.00	79	223	79.0	1.27	1.12	1.71	3	1.8	
		9/18	++	0	132	2.10	72	225	91.0	2.48	1.10	1.51	4	2.0	

* The cardiac output of this patient was determined by the venous plateau method.

Following the administration of the drug, the cardiac output tended to be higher in three subjects, lower in three subjects and unchanged in the remaining five. The arteriovenous oxygen difference was, in general, somewhat less in five subjects, slightly greater in two and unchanged in four.

Three subjects failed to show evidence of improvement following the administration of digitalis (table 3). One had a decrease in the cardiac output; another, an increase, and the third, no change.

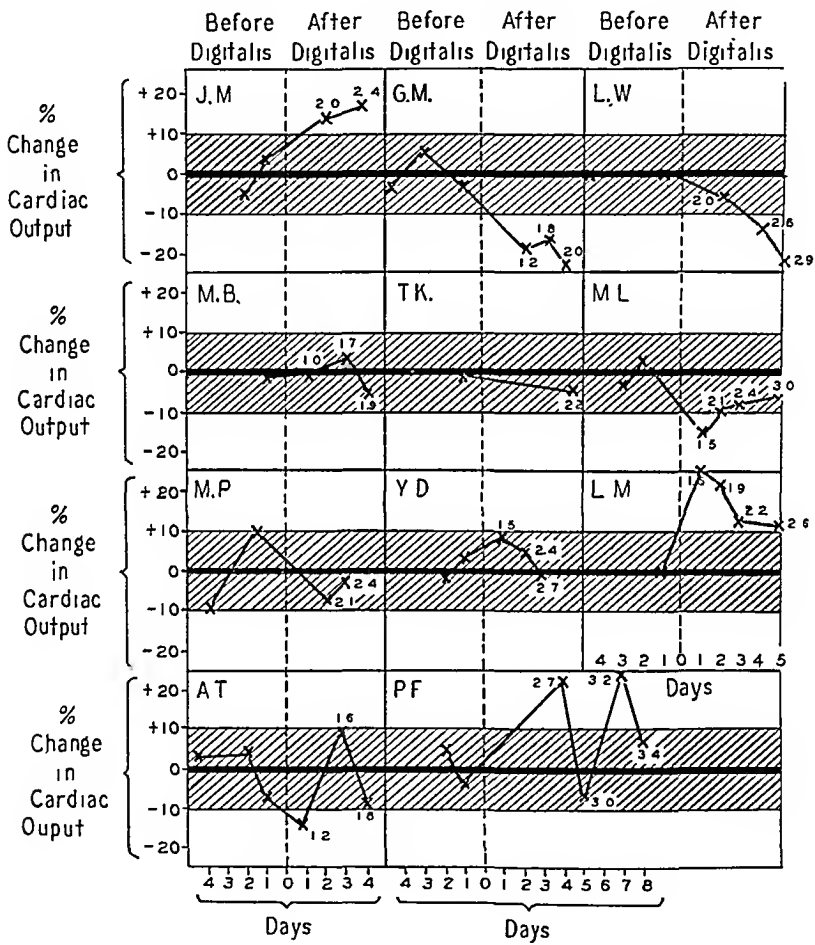


Chart 2.—The data are plotted for the subjects who exhibited questionable improvement following the administration of digitalis. The central bar represents the average value for the cardiac output before the administration of digitalis. Changes within 10 per cent of this are not considered significant. The numbers refer to the total amount (in grams) of digitalis received at the time of observation.

In the entire group of twenty-two patients five persons had an average increase of more than 10 per cent in the cardiac output per minute following treatment with digitalis. Improvement was definite in two, questionable in two and absent in one. Four patients had an

TABLE 3.—Observations on Patients Showing No Improvement After the Administration of Digitalis

Patient	Diagnosis	Date	Dyspnea	Edema	Weight, Pounds	Vital Capacity, Liters	Heart Rate	Oxygen Consumption per Minute, Cc.	Arterio-venous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Cardiac Output, Liters per 100 Cc. of Oxygen Absorbed	Cardiac Output per Minute, Square Meter	Duration of Administration of Digitalis, Days	Total Amount of Digitalis Given, Gm.
R. O.	Hypertension	1933	++	+	136	2.75	82	187	68.4	2.74	1.46	1.73	..	0
		2/18	++	+	136	2.70	88	178	73.7	2.41	1.36	1.57	..	0
		2/22	++	+	136	2.70	80	191	71.8	2.66	1.39	1.73	3	2.0
		2/25	++	+	136	2.70	91	165	83.4	1.98	1.20	1.20	4	2.3
		2/26	++	+	136	2.70	66	226	73.3	2.89	1.23	1.73	..	0
S. F.	Rheumatic aortic insufficiency	4/17	++	0	...	3.80	70	238	77.8	3.06	1.29	1.83	..	0
		4/18	++	0	...	3.65	70	243	64.4	3.77	1.55	2.26	1	1.5
		4/19	++	0	...	4.00	68	216	68.1	3.18	1.47	1.90	2	2.1
		4/20	++	0	...	4.13	67	207	66.7	3.10	1.50	1.86	3	2.4
		4/21	++	0	...	4.25	60	205	65.8	3.12	1.52	1.87	4	2.7
F. B.	Syphilitic aortic insufficiency	4/22	++	0	...	3.85	102.4	2.41	0.98	1.44	..	0
		7/15	+++	++	155	1.90	..	247	88.5	2.68	1.13	1.61	1	1.5
		7/18	+++	++	160	1.80	..	238	89.4	2.53	1.12	1.52	2	2.0
		7/19	+++	++	161	1.70	..	226	82.7	2.54	1.21	1.52	3	2.3
		7/20	+++	++	161	1.70	..	210

average decrease of more than 10 per cent in the cardiac output per minute. Improvement was definite in one, questionable in two and absent in one. Thirteen patients showed changes of less than 10 per cent in the average cardiac output following the administration of digitalis. Benefit was distinct in five of these, questionable in seven and absent in one. The output of the heart in proportion to the oxygen consumption of the body was increased after digitalis therapy in eight patients, beneficial effects being definite in two, questionable in four and not evident in two. The cardiac output was diminished in proportion to the metabolism in three subjects following digitalis therapy. Of these, one patient showed definite improvement and two were questionably better. The cardiac output was unchanged (i.e., changed by 10 per cent or less) in relation to the metabolism in eleven subjects. Definite improvement was noted in five, a questionably beneficial effect in five and no effect in one. The means of all the average values for the cardiac output and the arteriovenous oxygen difference were as follows: The cardiac output was 2.82 liters before the administration of digitalis and 2.81 liters after therapy. The arteriovenous oxygen difference was 87.1 cc. per liter of blood before the administration of digitalis and 83.7 cc. after digitalis therapy. We interpret the findings as indicating that digitalis has no consistent effect on the cardiac output of persons with congestive heart failure.

This conclusion is different from that arrived at by Stewart and Cohn.¹⁰ The disagreement can probably be attributed to the difference in the method employed for determining the cardiac output. Stewart and Cohn stated that their initial samples of gas were taken after fifteen seconds of rebreathing. In a previous study¹⁸ it has been shown that such a short time does not usually suffice to obtain a homogeneous mixture in the lung-bag system for patients with congestive heart failure. Of the eight patients studied by the hydrogen method by Grollman, Friedman, Clark and Harrison,¹⁸ an adequate mixture was obtained before twenty seconds of rebreathing in only two.

In an attempt to understand the difference between our results and those of Stewart and Cohn, we have made a number of measurements of the arteriovenous oxygen difference as determined according to the older technic with two samples used by them and according to the method requiring three samples, employed in the present study. Illustrative data are given in table 4. Ten such comparisons were made. In three instances false low results for the arteriovenous oxygen difference and false high results for the cardiac output were obtained when the samples were taken prematurely. In the remaining instances, too early sampling resulted in false high values for the arteriovenous oxygen difference and erroneously low values for the cardiac output. Furthermore, as illustrated by the first pairs of observations in table 4, agreement between

the results is not an adequate criterion of accuracy, as the arteriovenous oxygen difference obtained on successive rebreathings may agree and yet not be seriously inaccurate. Thus, when the samples are taken before a homogeneous mixture has been obtained in the lung-bag system, erroneous values for the arteriovenous oxygen difference and for the cardiac output are likely to be obtained. These observations seem to explain the discrepancy between our findings and those of Stewart and Cohn.

COMMENT

In some patients clinical improvement following the administration of digitalis is accompanied by an increase in the cardiac output. This

TABLE 4.—*Measurements of the Arteriovenous Oxygen Difference and Cardiac Output According to the Methods Employing Two Samples and Three Samples*

Comment	Erroneous Data			Correct Data			
	Time of Samples, Seconds	Arterio-venous Oxygen Difference, Cc. per Liter	Cardiac Output per Minute, Liters	Time of Samples, Seconds	Arteriovenous Oxygen Difference, Cc. per Liter		Cardiac Output per Minute, Liters
					First	Second	
Samples taken too soon giving inadequate mixture	15-19	81	2.9	18-21-25	59	63	3.9
	16-19	72	3.3				
	17-21	118	2.1	23-28-33	102	96	2.5
	17-21	125	2.0				
	17-21	166	1.8	21-26-31	97	94	3.1
	18-22	92	2.6	22-26-30	77	79	3.1
	19-24	94	1.6	24-28-32	77	71	2.1
	19-23	103	2.4	21-26-31	84	84	2.8
	18-24	108	2.2	20-25-30	93	87	2.7
	19-21	69	3.8	22-27-32	86	94	2.9
	20-24	82	2.5	24-28-32	107	100	2.0
	18-24	70	2.8	24-29-33	86	84	2.3

effect is probably due to the drug's action on the heart, for there is ample evidence from studies on the isolated heart and on the heart-lung preparation that the drug may under certain conditions increase the contractile power of the myocardium.

In other patients clinical improvement brought about by digitalis is associated with a decrease in the cardiac output per minute. Since such an effect is not usually observed in the isolated heart, it is reasonable to ascribe it to an action on the periphery, and there is much evidence in favor of such an assumption. Thus Dock and Tainter⁸ found that the decline in the cardiac output produced in normal dogs by digitalis was associated with, and apparently due to, a decrease in the venous pressure. Stewart and Cohn¹⁰ failed to find diminution in the venous pressure in normal persons and concluded that the diminished output was secondary to the decrease in the size of the heart. However,

Ryland²² has recently studied a larger group of subjects, and his work indicates that the drug does diminish the venous pressure of normal persons. It seems probable, therefore, that the decrease in cardiac output which occurred in several of our patients was due to a peripheral action of digitalis. Just how this is brought about is still questionable. Dock and Tainter⁸ found that the drug produced pooling of the blood in the portal system in experimental animals. The observations of Wollheim,²³ Schürmeyer²⁴ and Mies²⁵ indicated that digitalis causes diminution in the circulating blood volume not only in persons with cardiac disease but also in normal persons and in normal animals.

Many of our patients exhibited clinical improvement following digitalis therapy without showing a change in the cardiac output. It seems probable that in such instances the peripheral effect of the drug (tending to decrease the venous return) was balanced by the cardiac action (tending to increase the output). In any case, the results indicate that clinical improvement produced by digitalis cannot in general be ascribed to an increase in the blood supply to the tissues.

The one constant effect of digitalis on which all investigators have agreed, and which occurs in the isolated heart, in the heart-lung preparation, in normal animals, in animals with cardiac disorders, normal human beings and in human beings with congestive heart failure, is a diminution in the size of the heart. Congestive failure is invariably associated with dilatation, which leads to an increase in the venous pressure, and improvement is accompanied by a diminution in the degree of dilatation and by a fall in the venous pressure. As has been shown by Starling and Visscher,²⁶ the dilated heart is inefficient because it consumes more oxygen than does the normal organ in order to do a given amount of work. By enabling the heart to carry out its work with a smaller volume, i.e., by increasing the "fitness" and diminishing dilatation, digitalis increases cardiac efficiency. It seems probable that the heart is therefore able to perform the same amount of work with a smaller expenditure of energy and that this is the most important effect of digitalis. In patients with auricular fibrillation the diminution in heart rate and the elimination of pulse deficit after the administration of digitalis are of great importance, but these effects are often not apparent in persons with

22. Ryland, D. A.: The Effect of Digitalis on the Venous Pressure of Normal Individuals, *J. Clin. Investigation* **12**:847, 1933.

23. Wollheim, E.: Kompensation und Dekompensation des Kreislaufs, *Klin. Wchnschr.* **7**:1261, 1928.

24. Schürmeyer, A.: Ueber Blutmengenbestimmungen bei Herzfehlern, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*, 1928, p. 388.

25. Mies, H.: Ueber die Wirkung des Strophanthin auf die zirkulierende Blutmenge, *Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch.*, 1931, p. 208.

26. Starling, E. H., and Visscher, M.: The Regulation of the Energy Output of the Heart, *J. Physiol.* **62**:243, 1922.

regular rhythm. The increase in cardiac output after digitalis therapy may be of importance if the output has been previously markedly decreased, as occurs in certain patients with auricular fibrillation of sudden onset. In other cases, in which congestive failure occurs with a relatively normal output, the diminution of output following the administration of digitalis will tend to lessen the burden on the overloaded heart. However, since the most constant effect of the drug is on the size of the heart, it appears that benefit produced by it is to be ascribed in general to diminished dilatation, diminished expenditure of energy and increased efficiency.

SUMMARY

The effect of digitalis on the cardiac output of patients with congestive heart failure has been investigated by the acetylene method. Prior to the administration of digitalis, most of the subjects had subnormal values for the cardiac output.

Of twenty-two patients, three showed no improvement after the administration of the drug, ten had subjective benefit and eight exhibited definite objective improvement. In each of the groups some of the patients showed an increase in the cardiac output per minute, some a decrease and some no change. Consistent alterations of the cardiac output in proportion to the oxygen consumption were not observed.

PATHOLOGY OF THE VESSELS OF THE PULMONARY CIRCULATION

PART III

O. BRENNER, M.D., M.R.C.P.

Physician for Outpatients and Physician in Charge of the Cardiographic
Department, Queen's Hospital

BIRMINGHAM, ENGLAND

SECONDARY PULMONARY VASCULAR SCLEROSIS

DISTRIBUTION OF SCLEROSIS IN THE PULMONARY VASCULAR BED

It now seems desirable to discuss the distribution of sclerosis in the pulmonary vascular bed in the various etiologic groups. Tables 22 and 23 and figures 9 to 16 summarize the data obtained by averaging the degree of sclerosis noted in each etiologic group in the various divisions of the pulmonary vascular bed. Though this may be of some value in making a comparison of the various groups, it must be emphasized that since the grading of the sclerosis was according to arbitrary criteria, which necessarily differed with each type of vessel examined, the tables and figures show only in a general way the variations noted in the degree of sclerosis in the different divisions of the pulmonary vascular bed.

In the "no cause" group there were, if the case of primary sclerosis in a boy of 11 years is omitted, 15 cases in patients under 40, most of whom died of some acute infection. Sclerosis of some portion of the pulmonary vascular bed was present in all but 3. It was least frequent in the stem of the pulmonary artery and in the large veins and commonest in the large elastic arteries, arterioles, venules and small veins. Figure 9 shows that the average degree of sclerosis was small in all the divisions of the pulmonary vascular bed. The average curve did not differ markedly from the curves constructed for the individual cases in this group and so may be accepted as roughly indicating the distribution of sclerosis in the pulmonary vascular bed in the cases in this group.

All the patients over 40, even in the absence of factors known to raise the pulmonary arterial pressure, showed sclerosis of some portion of the pulmonary vascular bed. The distribution was similar to that

In this series of five papers the superior numbers refer to the bibliography which will be published in connection with the last paper. The superior letters refer to footnotes.

TABLE 22.—*Distribution of Sclerosis in the Pulmonary Vascular Bed in Patients Less Than 40 Years of Age**

Etologic Factor	Stem of Pulmonary Artery				Small Muscular Arteries				Arterioles and Venules				Small Veins				Large Intrapulmonary Veins				Main Extrapulmonary Veins			
	Num-ber		Per-cent-		Num-ber		Per-cent-		Num-ber		Per-cent-		Num-ber		Per-cent-		Num-ber		Per-cent-		Num-ber		Per-cent-	
	of with Pa-	tients†	rosi	s age	of with Pa-	tients†	rosi	s age	of with Pa-	tients†	rosi	s age	of with Pa-	tients†	rosi	s age	of with Pa-	tients†	rosi	s age	of with Pa-	tients†	rosi	s age
No cause	15	3	21	0.3+	10	67	0.9+	8	53	0.6+	12	80	1.1+	10	67	0.9+	3	23	0.2+	11	70	0.5+	1 lost	
Pulmonary disease	6	4	67	1.0+	5	100	1.4+	6	100	1.8+	6	100	2.8+	5	83	2.0+	1	20	0.2+	0	3 lost	
Cardiac disease	2	1	...	1.5+	2	...	3.0+	2	...	2.0+	2	...	3.0+	2	...	4.0+	2	...	3.5+	2	...	2.0+	2	...
Hypertension	3	1	...	0.5+	2	...	1.0+	2	...	1.0+	3	...	2.0+	2	...	1.7+	0	...	0
Pulmonary and cardiac disease	3	2	...	1.3+	2	...	0.7+	3	...	1.7+	3	...	3.0+	3	...	1.7+	3	...	2.3+	2	...	2.0+	1 lost	
Cardiac disease and hypertension
Pulmonary and cardiac disease and hypertension
Pulmonary disease and hypertension

* This table shows the number of patients with sclerosis and the average degree of sclerosis in each type of vessel in each etologic group.

† One patient with primary pulmonary vascular sclerosis is not included.

TABLE 23.—*Distribution of Sclerosis in the Pulmonary Vascular Bed in Patients Over 40 Years of Age**

Etiologic Factor	Stem of Pulmonary Artery						Large Elastic Arteries						Small Muscular Arteries						Arterioles and Venules						Small Veins						Large Intrapulmonary Veins						Main Extrapulmonary Veins																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
	Num-ber of Pa-tients	Num-ber of with Scler-osis	Per-cent- age	Deg-ree of Scler-osis	Num-ber with Scler-osis	Per-cent- age	Deg-ree of Scler-osis	Num-ber with Scler-osis	Per-cent- age	Deg-ree of Scler-osis	Num-ber with Scler-osis	Per-cent- age	Deg-ree of Scler-osis	Num-ber with Scler-osis	Per-cent- age	Deg-ree of Scler-osis	Num-ber with Scler-osis	Per-cent- age	Deg-ree of Scler-osis	Num-ber with Scler-osis	Per-cent- age	Deg-ree of Scler-osis	Num-ber with Scler-osis	Per-cent- age	Deg-ree of Scler-osis	Num-ber with Scler-osis	Per-cent- age	Deg-ree of Scler-osis	Num-ber with Scler-osis	Per-cent- age	Deg-ree of Scler-osis																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																					
No cause	15	7	50	0.6+	14	93	1.6+	14	93	1.6+	15	100	2.2+	15	100	1.6+	6	40	0.6+	2	33	0.3+	1 lost																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													

* This table shows the number of patients in each etiologic group and the average degree of sclerosis in each division of the pulmonary vascular bed in each etiologic group.

† This group includes all the patients with congestive heart failure irrespective of age.

in the patients under 40, and the curve of average severity ran roughly parallel, though at a somewhat higher level (fig. 9). It thus seems that sclerosis increases in frequency and severity with age in all parts of the pulmonary vascular bed except the main extrapulmonary pulmonary veins.

The "pulmonary disease" group was comprised of 29 cases. Six patients were over, and 23 under, 40. Tables 22 and 23 and figure 10

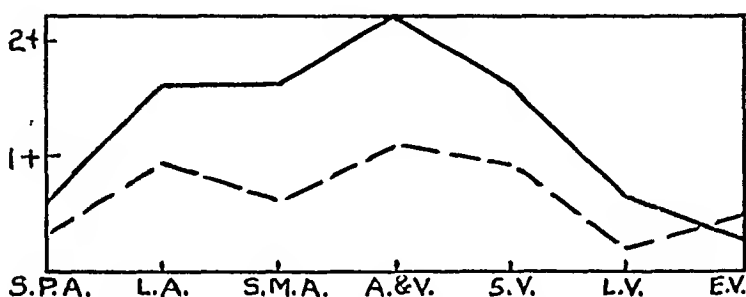


Fig. 9.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "no cause" group. In this chart and those that follow the dash line represents the patients under 40 and the solid line, the patients over 40 in the "no cause" group. S.P.A. indicates the stem of the pulmonary artery; L.A., large arteries; S.M.A., small muscular arteries; A.& V., arterioles and venules; S.V., small veins; L.V., large veins, and E.V., extrapulmonary veins.

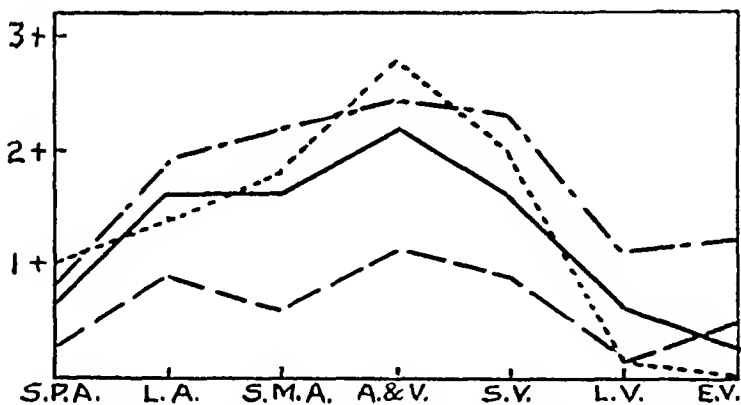


Fig. 10.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "pulmonary disease" group. The dotted line represents the patients under 40, and the dot-and-dash line, the patients over 40.

show the distribution and average severity of sclerosis throughout the pulmonary vascular bed in these cases. In all cases in patients under 40 sclerosis was present, and its average degree was greater than that in the corresponding cases in the "no cause" group except in the large intrapulmonary and extrapulmonary pulmonary veins. The marked sclerosis of the arterioles, venules and small veins was remarkable in view of the fact that the pressure in the veins might be expected, if anything, to be lower than normal. In all patients over 40 sclerosis was present in

some part of the pulmonary vascular bed. The curve of average severity ran parallel to and slightly above that in the cases of patients over 40 in the "no cause" group in all divisions of the pulmonary vascular bed, and the sclerosis was notably more severe than that in the "no cause" group in the large intrapulmonary and extrapulmonary pulmonary veins. The sclerosis reached its maximum, so far as the sclerosis in different portions of the pulmonary vascular bed could be compared, in the arterioles, venules and small veins.

The "cardiac disease" group was comprised of 7 cases. Two patients were under, and 5 were over, 40. Marked sclerosis was present throughout the pulmonary vascular bed in the patients under 40, both of whom died of congestive heart failure. The sclerosis was particularly marked in the venous portion of the pulmonary vascular

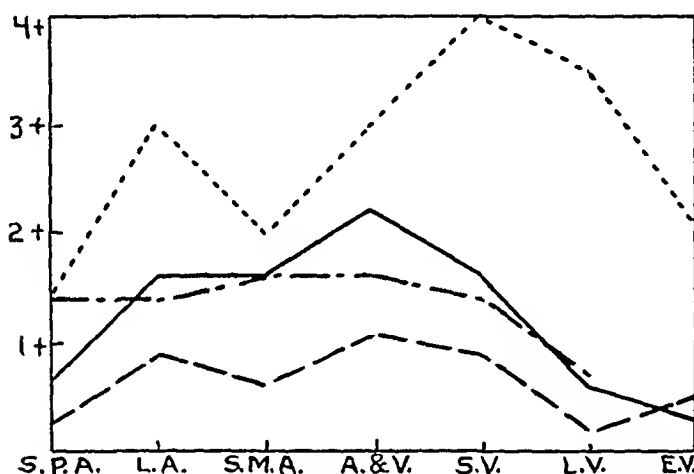


Fig. 11.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "cardiac disease" group. The dotted line represents the patients under 40, and the dot-and-dash line, the patients over 40.

bed and reached its maximum in the small veins, in which the average thickness of the walls was 25 per cent of the external diameter.

The 5 patients over 40 all had sclerosis of the coronary artery with cardiac hypertrophy but without heart failure. Figure 11 shows that the average degree of sclerosis was less than that in the "no cause" group in patients over 40 except in the stem of the pulmonary artery (there were not enough data as to the state of the extrapulmonary pulmonary veins); so it appears that cardiac disease without heart failure is not necessarily associated with a greater degree of sclerosis than may occur in otherwise normal elderly persons.

The "hypertension" group was comprised of 9 cases. Three patients were under, and 6 over, 40. All showed sclerosis in some part of the pulmonary vascular bed. Figure 12 shows that in the patients both

under and over 40 the degree of sclerosis was only slightly greater than that in the "no cause" group (except in the arterioles and venules and in patients under 40 in the small veins, where it was considerably greater), and that in the large veins it was, if anything, a little less than in the "no cause" group.

The "cardiac and pulmonary disease" group was comprised of 13 cases. Three patients were under, and 10 over, 40 (fig. 13). In

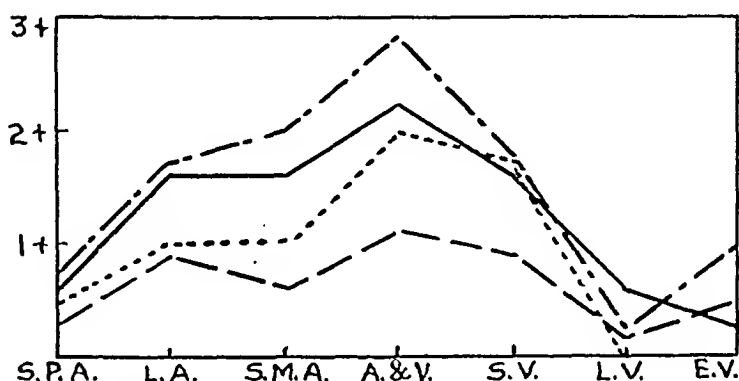


Fig. 12.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "hypertension" group. The dotted line represents the patients under 40, and the dot-and-dash line, the patients over 40 in the "hypertension" group.

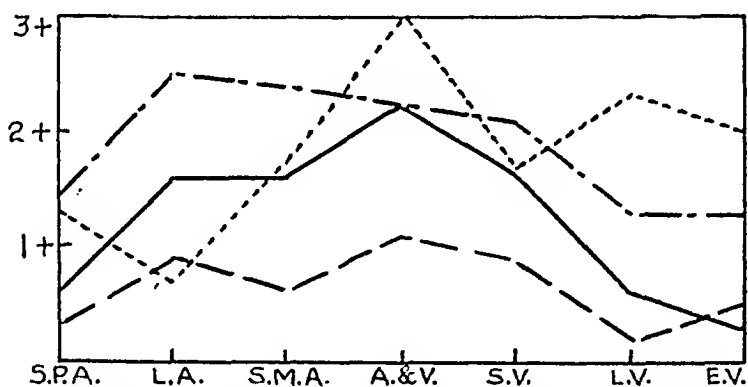


Fig. 13.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "pulmonary and cardiac disease" group. The dotted line represents the patients under 40, and the dot-and-dash line, the patients over 40.

those under 40 the average degree of sclerosis was slightly greater than that in the "no cause" group on the arterial, and considerably greater on the venous, side of the pulmonary vascular bed. Five of the 10 patients over 40 died of congestive heart failure. The general level of sclerosis was greater than that in the "no cause" group throughout the pulmonary vascular bed, on the arterial and venous sides, except in the arterioles and venules, where the sclerosis was the same as in

the "no cause" group. This group was remarkable for the relatively high degree of sclerosis in the large elastic arteries.

The "cardiac disease and hypertension" group consisted of 3 cases, all in patients over 40. Congestive heart failure was present in all. Figure 14 shows that the average degree of sclerosis was somewhat greater than in the "no cause" group in all parts of the pulmonary vascular bed.

The "cardiac and pulmonary disease and hypertension" group consisted of 3 cases. Two of the patients showed congestive heart failure. The average degree of sclerosis (fig. 15) was somewhat greater than

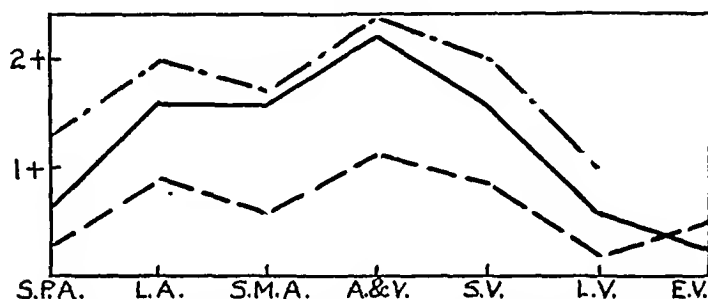


Fig. 14.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "cardiac disease and hypertension" group. The dot-and-dash line represents the patients over 40.

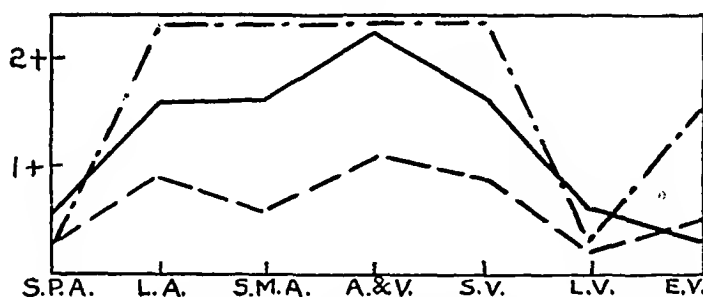


Fig. 15.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "pulmonary and cardiac disease and hypertension" group. The dot-and-dash line represents the patients over 40.

in the "no cause" group in all portions of the pulmonary vascular bed except the stem of the pulmonary artery and the large intrapulmonary veins, and the difference between the two etiologic groups was especially marked in the main extrapulmonary pulmonary veins.

The "pulmonary disease and hypertension" group consisted of 5 cases, all in patients over 40. Sclerosis was present in some part of the pulmonary vascular bed in all. The average degree of sclerosis was greatest (fig. 16) in the small muscular arteries and was greater than in the "no cause" group in all divisions of the pulmonary vascular bed,

particularly in the small muscular arteries and the extrapulmonary pulmonary veins.

Table 23 and figure 17 show the distribution and degree of sclerosis in the 25 patients of all ages with congestive heart failure. The average degree of sclerosis was greater than that in the "no cause" group in each division of the pulmonary vascular bed, particularly in the veins, large and small, but in each portion of the pulmonary vascular bed the changes were more severe in some one etiologic group than in the cases of congestive heart failure.

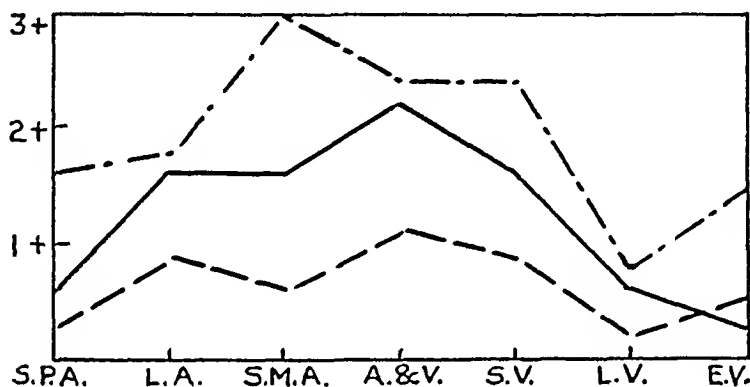


Fig. 16.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "pulmonary disease and hypertension" group. The dot-and-dash line represents the patients over 40.

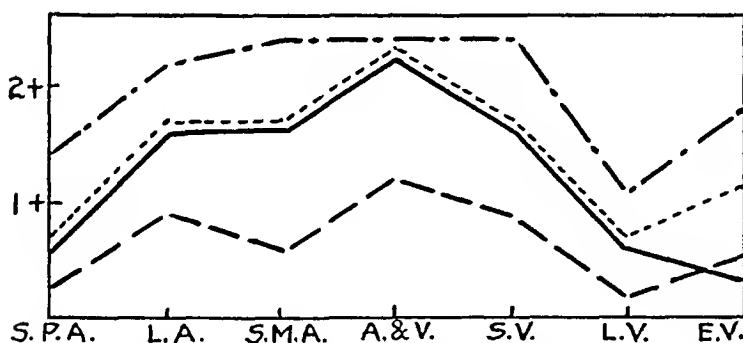


Fig. 17.—Graph showing the average degree of sclerosis found throughout the pulmonary vascular bed in the "congestive heart failure" group. The dot-and-dash line represents all the patients with heart failure, and the dotted line, all the patients without heart failure.

Thus, sclerosis increased in frequency and severity with increasing age in all divisions of the pulmonary vascular bed except the main extrapulmonary pulmonary veins, even in the absence of factors which are thought to raise the pulmonary venous pressure. The presence of such factors was associated with a slightly increased severity of sclerosis in all divisions of the pulmonary vascular bed, including the veins in the "pulmonary disease" group, in which it might be expected that the

blood pressure in the pulmonary veins would be low. The sclerosis was usually most marked in the arterioles, venules and small veins. In the various etiologic groups including cases of congestive heart failure and in the cases of congestive heart failure that have been reported, there was an especially heavy incidence of sclerosis on the venous side of the pulmonary vascular bed.

CHANGES IN THE HEART

Since there is no means of ascertaining the pulmonary blood pressure in man, the thickness of the right ventricle may be taken as a rough index, though it must be remembered that incompetence of the tricuspid valve as well as hypertension of the pulmonary vessels may cause hypertrophy of the right ventricle, and that, as in the systemic circulation, the degree of hypertrophy is not necessarily proportionate to the degree of hypertension. Hypertrophy of the right ventricle also occurs for unknown reasons (e.g., in cases of systemic hypertension or aortic incompetence, without evidence of heart failure¹⁷¹), and Lewis¹⁷¹ has stated that ventricular hypertrophy must not be taken as certain evidence of excessive work on the part of the ventricle. Nevertheless, the thickness of the right ventricle is the only available index of overstrain of the right ventricle, and it has been used with a full realization of the necessary limitations. In view of these limitations it was not thought necessary to undertake the task of separating the ventricles and weighing them independently. It was thought sufficient merely to measure the thickness of the ventricular walls and to pay no attention to the degree of dilatation of the cavity. A thickness up to 4 mm. was considered normal, from 4 to 6 mm. moderate hypertrophy and over 6 mm. great hypertrophy.

In most of the cases of pulmonary arteriosclerosis reported in the literature the right ventricle was hypertrophied, either with or without dilatation,^x or merely dilated or enlarged.^y This was probably because only isolated cases have usually been reported, with unexplained congestive heart failure or hypertrophy of the right ventricle, and the pulmonary arteries have been examined to find an explanation. Kisch¹⁴⁷ carefully examined 25 hearts showing hypertrophy of the right ventricle taken from patients who had had chronic pulmonary disease and other diseases but no independent cardiac disease or systemic hypertension. He weighed the ventricles separately and measured their thickness and the volume of the cavities. In 10 cases only the right ventricle and in 15 the whole right side of the heart was hypertrophied. None of the first group and all of the second showed chronic venous con-

(x) 47, 102, 106, 113, 174, 193, 202, 204, 226, 252, 262, 276, 288, 308, 331.

(y) 182, 186, 250, 262.

gestion in the systemic circulation. The left ventricle was hypertrophied in none of the first group and in 4 of the second. This he attributed to transmission of the venous hypertension back through the capillaries to the systemic arteries, but that appears unlikely; at all events it should have caused systemic hypertension, but with the exception of a blood pressure of 160 in 1 patient hypertension was absent. The right ventricle was dilated in 5 patients in the first and 14 in the second group. At first only the "outflow path" is hypertrophied and dilated (i. e., from the apex of the right ventricle to the orifice of the pulmonary artery). Later the "inflow path," from the tricuspid orifice to the apex of the right ventricle, also dilates and hypertrophies. Usually, even when there was hypertrophy of the right auricle, there was no dilatation of the tricuspid valve, but the pulmonary orifice was dilated in 11 of the 25 cases.

In many of Giroux's ¹¹⁴ cases of pulmonary tuberculosis with pulmonary arteriosclerosis there was no hypertrophy of the right ventricle. Boas ³⁴ noted in 97 cases of pulmonary tuberculosis that the electrocardiogram showed preponderance of the right ventricle in 29 per cent and preponderance of the left ventricle in 30 per cent. Preponderance of the right ventricle was found chiefly in the younger patients, and there was no excessive tendency of the patients with fibrosis of the lungs to show this preponderance. Dubrow ⁸³ noted after thoracoplasty in dogs that the T wave in lead III tended to become negative (which he interpreted as evidence of strain on the right ventricle) and that at autopsy the right ventricle contained more fat than normal.

In the present series the right ventricle was normally thick in 53 cases, moderately thickened in 35 and greatly thickened in 10. In 2 cases the thickness was not recorded. Age and sex made no difference. Tables 24 and 25 show the relationship of the etiologic factors to the thickness of the right ventricle. The "no cause" group contained the largest proportion of cases in which the right ventricle was normal, but it also contained 2 cases (7 per cent), including that of the boy of 11 with primary pulmonary vascular sclerosis, in which there was great hypertrophy of the right ventricle. The right ventricle was normal least frequently in the "cardiac disease," "hypertension," "cardiac and pulmonary disease" and "pulmonary and cardiac disease and hypertension" groups, and it was greatly thickened most frequently in the same groups. Table 25, which gives analyses of the etiologic groups, shows that pleural adhesions and pulmonary abscess were not associated with hypertrophy of the right ventricle, while in cases of cardiac disease hypertrophy of the right ventricle was least common in cases of sclerosis of the coronary artery without congestive heart failure and was most common in cases of rheumatic cardiac disease and syphilitic aortitis. The frequency of great hypertrophy of the right ventricle in

cases of systemic hypertension is noteworthy and has been commented on by others.² The cause is not clear. The hypertrophy may occur

TABLE 24.—*Relationship of the Thickness of the Right Ventricle to the Etiologic Factor*

Etiologic Factor	Num- ber of Pa- tients	Patients with a Normal Right Ventricle (up to 4 Mm.)		Patients with a Moderately Thickened Right Ventricle (Between 4 and 6 Mm.)		Patients with a Greatly Thickened Right Ventricle (Over 6 Mm.)	
		Num- ber	Per- cent- age	Num- ber	Per- cent- age	Num- ber	Per- cent- age
No cause	30	24	80	4	13	2	7
Pulmonary disease	29	18	62	11	38
Cardiac disease	7	2	29	3	43	2	29
Hypertension	9	1	11	5	56	3	33
Pulmonary and cardiac disease.....	12	4	33	6	50	2	17
Cardiac disease and hypertension.....	3	3	100
Pulmonary and cardiac disease and hypertension	3	1	33	1	33	1	33
Pulmonary disease and hypertension.....	5	3	60	2	40

TABLE 25.—*Further Analysis of the Relationship of the Etiologic Factor to the Thickness of the Right Ventricle*

Etiologic Factor		Number of Pa- tients	Normal Right Ventricle		Moderately Thickened Right Ventricle		Greatly Thickened Right Ventricle	
			Num- ber	Per- cent- age	Num- ber	Per- cent- age	Num- ber	Per- cent- age
A. Pulmonary dis- ease (isolated or combined with cardiac disease or hypertension)	Bronchitis alone.....	1	1
	Emphysema alone...	26	14	54	10	38	2	7
	Fibrosis of lungs.....	4	3	..	1
	Emphysema and fi- brosis	12	5	42	6	50	1	8
	Abscess.....	4	4	100
B. Pleural adhesions (in patients in "no cause" group)	No adhesions.....	16	13	81	1	6	2	13
	Patchy adhesions....	11	8	73	3	27
	Patchy adhesions on one side; universally adherent on the other	1	1
	Both pleural obliter- ated
C. Heart disease (alone or com- bined with pul- monary disease or hypertension)	Rheumatic with mi- tral disease	2	1	..	1	..
	Rheumatic, mitral and aortic disease	3	1	..	1	..	1	..
	Aortic stenosis (iso- lated)	1	1	..
	Coronary arterioscle- rosis with cardiac hypertrophy	16	6	38	7	43	3	19
	Syphilitic.....	9	2	22	5	56	2	22
	Idiopathic hyper- trophy	1	1
	Pericarditis.....	1	1

without congestive heart failure. It has been attributed to an increased blood flow in the coronary artery. Possibly there is a simultaneous

(s) 17, 1, 176.

hypertension of the pulmonary vessels due to the same cause as the systemic hypertension.

Table 26 and figure 18 show that while in general the greater the thickness of the right ventricle the greater the sclerosis throughout the pulmonary vascular bed, the difference was slight and did not hold for all portions of the pulmonary vascular bed. Moreover, the table and figure represent average figures, and the correspondence in individual cases was even less close. It must therefore be concluded either that the thickness of the right ventricle is an imperfect guide to the

TABLE 26.—*Relationship of the Degree of Sclerosis in the Pulmonary Vascular Bed to the Thickness of the Right Ventricle*

Thickness of Right Ventricle	Number of Patients	Stem of Pulmonary Artery	Large Elastic Arteries	Small Muscular Arteries	Arterioles and Venules	Small Veins	Large Veins	Extra-pulmonary Pulmonary Veins
Normal.....	53	0.7+	1.6+	1.8+	2.0+	1.8+	1.0+	1.1+
Moderately thickened....	35	0.9+	1.9+	1.9+	2.4+	1.9+	0.8+	1.2+
Greatly thickened.....	10	1.2+	2.2+	2.0+	2.1+	2.0+	1.4+	1.5+

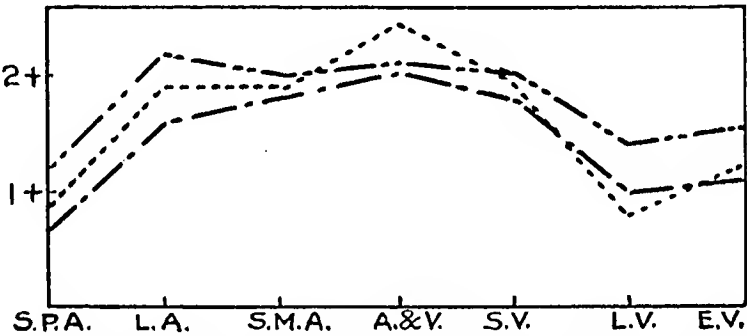


Fig. 18.—Graph showing the relationship of the degree of thickness of the right ventricle to the degree of sclerosis in the pulmonary vascular bed. The dot-and-dash line represents normal thickness; the dotted line, moderate thickness, and the two-dots-and-dash line, great thickness, of the right ventricle.

height of the pulmonary arterial pressure or that a raised pulmonary arterial pressure is not the only cause of pulmonary vascular sclerosis.

ETIOLOGY OF SECONDARY PULMONARY VASCULAR SCLEROSIS

The bearing of the facts previously discussed on the pathogenesis of pulmonary arteriosclerosis will now be considered. This must be done in connection with the question of the pathogenesis of arteriosclerosis in general. Attempts to isolate the problem of pulmonary arteriosclerosis must inevitably fail.

1. *Age*.—In elderly persons systemic arteriosclerosis is practically constant. Wells ³²¹ said that in old age the colloids of the elastic fibers of the aortic media lose water and become less dispersed and more

granular. Aschoff¹⁴ said that products of wear and tear accumulate and are precipitated and that an increase in the fibrous tissue in the intima and media normally occurs. Therefore, the arteries of the aged normally become rigid, inelastic, elongated, dilated and tortuous. Many writers^a have said that this is an important predisposing cause of sclerosis. The blood stream is slowed in the dilated arteries, and this, in some unspecified manner (Thoma), causes proliferation of the intimal elastic tissue, which tends to restore the lumen to its original size and the blood flow to its original velocity. This teleologic theory does not account for the many cases in which sclerosis not only restores the lumen to normal but narrows it almost to the point of obliteration. In the present state of knowledge it is probably best to ascribe senile arteriosclerosis to the "wear and tear of a long life," a phrase which at least has the merit of being broad enough to cover any information which may be gained in the future.

Most of the few observers who have studied sclerosis in the pulmonary circulation have agreed that it increases with age. Fischer¹⁰³ expressed the belief that it is due to the presence of senile emphysema, but no one else has agreed with him. Ljungdahl¹⁷⁶ observed macroscopic sclerosis in 50 per cent of 52 patients over 50 with no condition likely to raise the pulmonary blood pressure, and microscopic sclerosis in 58 per cent. Wartman⁸¹² noted in routine sections made in 426 consecutive autopsies that slight sclerosis was present in 6.4 per cent of males under 30 and slight sclerosis in 8.6 per cent and severe sclerosis in 2.9 per cent of females, while in persons over 60 slight sclerosis was present in 41.6 per cent of males and 22.2 per cent of females and severe sclerosis in 16.9 per cent of males and 17.5 per cent of females.

In the present series the influence of age is shown in figure 9 and tables 4 to 23. Excluding 1 patient with primary sclerosis, there were 15 patients under 40 and 15 over 40 in whom there was no reason to expect a raised pressure in the pulmonary vessels. Slight sclerosis was present in all portions of the pulmonary vascular bed in most of the patients under 40 (except in the stem of the pulmonary artery and the large veins, which were only occasionally involved); sclerosis was present in every patient over 40 and was usually more severe in every portion of the pulmonary vascular bed. The fact that sclerosis is so common in youth shows that age per se is not the cause; but the fact that it is commoner and more severe in later life suggests that it is due to some factor or factors which act continuously or at intervals throughout life, so that exposure to these factors increases with age.

2. *Changes in the Vasa Vasorum*.—Such changes have been held responsible, though this theory is unlikely because the vasa vasorum

(a) 237, 321.

supply only the outer third of the media, the inner two-thirds and all the intima being supplied from the lumen of the vessel. Posselt²⁴⁰ suggested that in cases of mitral stenosis the pulmonary artery is stretched and that there are narrowing of the vasa, atrophy of the tissue supplied by them and secondary sclerosis of the overlying intima. Mair¹⁹³ suggested that in his case the sclerosis may have been secondary to sclerosis of the bronchial vessels, from which the vasa are derived. In the present series the bronchial arteries and vasa vasorum often showed sclerosis, but no relationship could be traced to the sclerosis of the pulmonary vessels. In view of the lack of evidence that systemic arteriosclerosis is due to disease of the vasa, it must be concluded that pulmonary vascular sclerosis is not due to sclerosis of the bronchial arteries or of the vasa vasorum.

3. *Infection*.—Most observers have found no evidence that infection causes arteriosclerosis.^b Some^c have expressed the belief that infection possibly may act indirectly by disturbing the cholesterol metabolism or vasomotor tone. Others^d have said that infection is important. Posselt²⁴⁰ said that 3 of his own 10 patients had smallpox in their youth. Some writers^e have contended that in cases of mitral stenosis infection, probably rheumatic, as well as hypertension of the pulmonary vessels is important in causing the sclerosis. In two instances Zeek²³² observed pulmonary arteriosclerosis in the stillborn fetus of a septic mother. Wiesel^f described edema and necrosis followed by fibrosis in the media of systemic and pulmonary vessels in cases of infection and considered that these predispose to true arteriosclerosis. It should be noted that the changes described by Wiesel were not those of arteriosclerosis and that the evidence of others depended on insufficient statistical material or erroneous interpretation of histologic appearances. In the present series no correlation between infection and the occurrence of arteriosclerosis could be made out, and it would be difficult to prove that any connection existed, since both pulmonary arteriosclerosis and infection in the past history were almost universally present. The histologic changes were those of a degenerative, not an inflammatory, lesion from the earliest stages at which they could be recognized. The only point favoring the theory of a connection with infection was that sometimes the changes were most marked near local changes in the lungs, such as chronic abscesses, foci of tuberculosis and patches of fibrosis.

(b) 138, 176, 188, 213.

(c) 14, 138.

(d) 96, 161, 186, 240, 295, 324, 325, 331, 332, 333.

(e) 161, 295, 304.

(f) 324, 325.

4. *Poisons*.—Poisons, such as alcohol, tobacco and lead, have been blamed.⁸ Aschoff suggested that they may act by causing changes in the metabolism or in the vasomotor tone. Kitamura described a case of pulmonary arteriosclerosis in a patient who drank beer excessively, but attributed the sclerosis to plethora rather than to the toxic effects of alcohol. Macnider gave rabbits 50 cc. of a 20 per cent solution of alcohol daily and noted that in 9 of the 13 animals intimal lesions developed that resembled atherosclerosis, together with round cell infiltration of the media, but that similar lesions were present in 3 of the 16 controls. Thus, there is no good evidence that arteriosclerosis in general or pulmonary arteriosclerosis in particular is due to the action of toxins.

5. *Hormones*.—Anitschkow⁶ said that castration and thyroidectomy facilitate the experimental production of atheroma by means of diet containing cholesterol, while the administration of thyroid makes it more difficult. Aschoff¹⁴ suggested that the lipemia of diabetes and the hypocalcemia of tetany may play a part. Systemic arteriosclerosis is common in cases of diabetes, but Ljungdahl¹⁷⁶ observed pulmonary arteriosclerosis in only 1 of 6 young diabetic patients.

6. *Nervous Influences*.—Harris¹²⁶ observed that section of the cervical portion of the sympathetic trunk in rabbits caused endarteritis obliterans of the arteries of the ear, fragmentation of the elastica and hyperplasia of the media followed by patchy atrophy and fibrosis. Shaw²⁷⁹ reported that irritation of the cervical vagus and sympathetic nerves caused aortic atheroma in 20 of 25 rabbits. Similar lesions were present in only 1 of 22 controls. Stopford²⁹¹ said that continuous irritation of the brachial plexus by a cervical rib causes intense spasms of the arteries of the limb and of their vasa vasorum, which result in intimal thickening, patchy endothelial destruction and thrombosis with organization and recanalization. However, there is no sufficient evidence that such processes play a part in the production of the ordinary systemic or pulmonary arteriosclerosis.

7. *Direct Irritation of the Vessels*.—In some of Brüning's⁴⁸ cases particles of coal dust were present in the walls of some of the sclerotic vessels. In Rosenthal's²⁵⁶ cases of pneumoconiosis it was suggested that the dust particles destroyed many pulmonary capillaries and initiated the arterial changes. In Macaigne's¹⁸⁶ case fungus filaments grew into the arterial walls and appeared to initiate the *thrombo-artérite*. Such factors can rarely, if ever, be the cause of pulmonary arteriosclerosis.

8. *Cholesterol Metabolism*.—In rabbits fed cholesterol Anitschkow noted deposits of cholesterol in the aortic intima, at the origin of branches and other sites characteristic of natural atheroma, and in the pulmonary artery and great veins. If the cholesterol feeding was stopped, the intimal cholesterol gradually disappeared, but thickened fibrous patches were left. Clarkson⁵⁸ observed that feeding rabbits on a diet with a high protein and low fat content produced atheroma, and that the rabbits showed evidence of hypercholesterolemia. Aschoff¹¹ expressed the belief that the primary change is the infiltration into the intima of lipid-containing plasma and the deposition of cholesterol. In children but not in adults the lipid may be reabsorbed. The lipid content of the diet does not affect the occurrence of atheroma but determines the amount of cholesterol in the plaques. Roger²⁵³ said that the pulmonary arterioles are especially concerned in fat metabolism, so that they should be particularly prone to be arteriosclerotic. Any fat that is liberated into the systemic circulation (e. g., after a fatty meal) tends to be arrested in the pulmonary arterioles, where it is absorbed and destroyed by the endothelial cells. MacMahon¹⁹⁰ reported a case of alcoholic fatty liver, with hepatic destruction due to carbon tetrachloride poisoning and liberation of the fat into the blood. At autopsy the blood of the right side of the heart and pulmonary arteries contained a great deal of fat, which rose to the surface on standing, while that of the pulmonary veins and left side of the heart contained none. The earliest histologic change is the deposition of cholesterol in the intima, followed by connective tissue proliferation superficial to this.

There is thus no doubt as to the importance of the deposition of cholesterol, though whether it is primary or secondary has not been determined. Roger's work suggested that the pulmonary vessels are particularly closely concerned in lipid metabolism, but it should be noted that atheroma has thus far been produced by cholesterol feeding only in herbivorous animals on a diet foreign to them.

9. *Constitutional Inferiority*.—A constitutional inferiority of the material of which the arteries are composed has been suggested as a cause of marked pulmonary arteriosclerosis in the absence of factors likely to raise the pulmonary arterial pressure markedly, a suggestion which can be neither proved nor disproved, though Posselt²⁴⁰ said that the small left ventricle, hypoplastic aorta and narrow pulmonary veins seen in some cases of pulmonary vascular sclerosis indicate the poor quality of the vascular system and Wätjen³⁰⁸ described sinus-like dilatations of the pulmonary arteries in his case of vascular sclerosis in an infant of 11 months with congenital cardiac disease. There is thus

little evidence that inferiority of the "vital rubber" is a factor, and even if it were, this explanation could not be thought satisfactory until it had been shown in what the inferiority consists.

10. *Pulmonary Vascular Hypertension*.—This is thought by most to be the chief factor, but chiefly because pulmonary vascular sclerosis is rarely looked for in cases in which there is no mitral stenosis, etc. Steinberg²⁸⁴ noted gross sclerosis in 62 per cent of cases in which there was no obstruction to the pulmonary circulation and in 82 per cent of cases in which there was obstruction (mitral stenosis, emphysema, etc.). Moschowitz¹ expressed the belief that pulmonary arterial hypertension is the cause of the sclerosis and said that in cases of mitral stenosis the veins as well as the arteries are sclerotic, while in cases of emphysema, in which the obstruction is preavenous (in the capillaries), the veins do not show sclerosis—a statement with which it is impossible to agree. Evans¹⁰² described a case of collapse of the right lung in which the vessels in the collapsed lung were normal while in the normal left lung there was marked arteriosclerosis. This he interpreted as indicating that collapse prevented the entry of an adequate amount of blood into the right lung, so that the pressure there was low. It is difficult to believe, however, that there could have been a significant difference in pressure in the two lungs, at least in the large vessels.

The influence of hypertension in the development of systemic arteriosclerosis is not clear. Allbutt⁴ said that in more than 50 per cent of cases of arteriosclerosis the blood pressure is not raised, and that in cases of long-standing hypertension the arteries may be normal.

At this point it seems opportune to examine the various factors which are generally thought to raise the pulmonary blood pressure.

A. Chronic Pulmonary Disease: The following conditions are of interest: 1. *Emphysema*. The effect of emphysema on the blood flow through the lungs is doubtful, as indicated in the section on pathologic physiology, and in many cases the right ventricle is of normal thickness. The reserve of pulmonary capillaries is so great that probably only the most extreme emphysema increases the resistance to blood flow through the lungs. Alexander³ noted evidences of preponderance of the right ventricle in the electrocardiograms of only 3 of 50 patients with long-standing asthma with emphysema, and 1 of these patients showed mitral stenosis also.

The importance of emphysema in producing pulmonary vascular sclerosis is disputed. Some^j have stated that sclerosis is no commoner in patients with emphysema than in patients of the same age without emphysema. Fischer¹⁰³ said that sclerosis is always present in cases

(i) 212, 213, 214.

(j) 64, 176, 240, 331.

of emphysema and that sclerosis occurs in the aged only in the presence of emphysema. Steinberg²⁸⁴ observed sclerosis in 86 per cent of patients with emphysema, as compared with 62 per cent of patients without pulmonary or cardiac disease. Again, some observers who have admitted the coexistence of emphysema and pulmonary vascular disease have stated that the arterial lesions are primary and that the emphysema is secondary, just as in cases of primary contracted kidney the renal lesions are secondary to the arterial lesions.^k

2. Pulmonary fibrosis. The means by which pulmonary fibrosis may obstruct the pulmonary circulation are discussed in the section on pathologic physiology. It seems probable that only the most extreme fibrosis could be effective and that therefore it is doubtful whether pulmonary fibrosis is important in raising the pulmonary blood pressure.

3. Pleural adhesions. These have been thought to interfere with the respiratory movements and so to throw a strain on the right ventricle, but it is doubtful if this is important in causing pulmonary vascular sclerosis.

4. Pulmonary tuberculosis. This may act by the absorption of toxins or by causing pulmonary fibrosis, compensatory emphysema and pleural adhesions. There is little evidence, however, that it ever causes a marked rise in the pulmonary blood pressure or that it is important in the production of sclerosis.

5. Neoplasm. Fried¹⁰⁷ said that vessels near masses of growth often are thickened, either by tumor invasion or by degenerative changes. Rössle²⁵² described a case in which many arteries with deposits of growth in the perivascular lymphatic vessels showed marked sclerosis. Hornowski¹³⁰ and Lutembacher¹⁸² each described a case in which a main pulmonary artery was narrowed by a mediastinal mass of growth, the right ventricle was hypertrophied, and the pulmonary vessels were sclerotic. This evidence is not enough to establish neoplasm or compression of the pulmonary artery as a cause of pulmonary vascular sclerosis.

6. Thoracic deformities. These are often said to be the cause of failure of the right heart and of pulmonary vascular sclerosis. Edeiken⁹¹ said that in cases of kyphoscoliosis one lung is compressed and may be fibrosed while the other shows compensatory emphysema, which further embarrasses the heart. The respiratory movements are restricted, and the growth of the chest lags behind that of the rest of the body. The vital capacity is reduced by from 20 to 60 per cent. But in 26 cases of kyphoscoliosis he noted evidence of preponderance of the right ventricle in electrocardiograms only once. Ljungdahl¹⁷⁶ observed sclerosis

(k) 96, 193, 215.

in 4 or 5 cases of kyphoscoliosis. The theory as to the importance of thoracic deformities in raising the pulmonary blood pressure and causing pulmonary vascular sclerosis therefore needs further investigation before it can be accepted.

In the present series there were 29 cases of uncomplicated pulmonary disease (emphysema with or without fibrosis and chronic tuberculosis). Figure 10 and tables 22 and 23 show that in patients under 40 the sclerosis was greater in all portions of the pulmonary vascular bed (including the small veins), except the large veins, than in the "no cause" group, while in patients over 40 the sclerosis was greater in the veins as well as the arteries than in the "no cause" group. Since in cases of pulmonary disease the obstruction is in the capillaries, it might be expected that, even if the pulmonary arterial pressure is raised, the venous pressure would be lowered, so that it is difficult to accept a simple mechanical explanation for the sclerosis. It has been pointed out that in some cases in which there are localized lesions of the lung (chronic abscess, fibrocaseous tuberculosis or fibrosis) the vascular lesions may be confined to the neighborhood of the pulmonary lesions.

Thus it seems that only in extremely advanced cases of pulmonary disease is the pulmonary circulation likely to be seriously obstructed. Nevertheless, the present investigation confirms previous ones in showing an increased frequency and severity of pulmonary vascular sclerosis in the presence of chronic pulmonary disease, though the incidence even without pulmonary disease is so great as to make the interpretation difficult, and the fact that veins as well as arteries share in the increased sclerosis makes it impossible to accept increased blood pressure as the only cause.

B. Chronic Cardiac Disease: In cases of congestive heart failure the left side of the heart usually fails before the right side, and the pressure in the pulmonary vascular bed rises more in the veins than in the arteries, since distensibility of the capillaries prevents the full rise in pressure from being transmitted back to the arteries. Ljungdahl¹⁷⁶ said that pulmonary vascular sclerosis is always present in cases in which there is stasis in the pulmonary circulation. Costa¹ observed sclerosis in only 18 of 25 cases of mitral stenosis. Miller²⁰³ observed sclerosis in only 15 of 52 cases of mitral stenosis, but his figures were obtained from routine autopsy notes and are therefore valueless. Zeek³³² observed sclerosis in 59 of 62 cases of rheumatic cardiac disease, and in 9 of these it was severe. Steinberg²⁸⁴ observed gross sclerosis in 29 of 35 cases of mitral stenosis (83 per cent), and in only 1 of these (3 per cent) was it severe. He observed sclerosis in 88 per cent of 68 cases of cardiac disease of all varieties, compared with 62 per cent

of cases in which there was no obstruction to the pulmonary circulation. Pulmonary vascular sclerosis has also been described in types of congenital cardiac disease, such as patency of the ductus arteriosus or of the interventricular septum, in which the aortic pressure is transmitted to the pulmonary artery.^m But Posselt²⁴⁰ also noted that in 4 per cent of his cases of pulmonary sclerosis, pulmonary stenosis, which might be expected to lower the pulmonary vascular pressure, was present.

In the cases of patients over 40 in the present series (fig. 11 and tables 6 to 23) the sclerosis in the "cardiac disease" group (sclerosis of the coronary artery and cardiac hypertrophy without congestive heart failure) was no greater than in the "no cause" group, though sclerosis was present in some part of the pulmonary vascular bed in all cases. The 2 patients under 40 both died of congestive failure, and in these cases the sclerosis was much greater than in the "no cause" group, particularly on the venous side. Thus, cardiac disease per se does not influence the frequency and severity of pulmonary vascular sclerosis, but if congestive heart failure is present, the frequency and severity of the sclerosis are increased in all parts of the pulmonary vascular bed (fig. 17).

C. Systemic Hypertension: Probably a transient rise in the systemic blood pressure does not cause a mechanical rise of pulmonary vascular pressure (see section on pathologic physiology), but it is possible that in cases of permanent hypertension there may be a spasm of the pulmonary as well as of the systemic arterioles, and pulmonary vascular hypertension may thus be caused. However, this seems improbable, since it is unlikely that the contraction of the pulmonary arterioles is of great importance in regulating the pulmonary blood pressure. Nevertheless, in many patients with systemic hypertension, even without heart failure, the right ventricle as well as the left was hypertrophied (table 24). Tables 6 to 23 and figure 12 show that while in patients under 40 the sclerosis was greater in all divisions of the pulmonary vascular bed than in the "no cause" group (this was probably chiefly because the "no cause" group included many cases in children and the "hypertensive" group, none), there was comparatively little difference in patients over 40. The cause of the common hypertrophy of the right ventricle in cases of systemic hypertension thus remains unknown, and there is no evidence that systemic hypertension is a factor in causing pulmonary vascular sclerosis.

Thus, all that can be said with confidence is that pulmonary vascular sclerosis increases in frequency and severity with the age of the patient and that factors which raise the pulmonary vascular pressure somewhat increase the frequency and severity of sclerosis in both pul-

(m) 174, 176, 240, 308.

monary arteries and veins. Pulmonary vascular sclerosis is practically as common as systemic vascular sclerosis and is constant in patients over 40. It is this universality which makes it so difficult to point to any one specific cause, though, as with systemic arteriosclerosis, the importance of age and hypertension as accessory factors seems fairly clear.

SYMPTOMS

It is obviously extremely difficult to differentiate the symptoms of secondary pulmonary vascular sclerosis from those of chronic pulmonary or cardiac disease which it complicates. Nevertheless, a great deal that seems singularly uncritical has been written on the symptoms. In the present series of 100 consecutive cases sclerosis was present in 97. Circulatory symptoms were present during life in only 25, and in all except 1 (a most unusual case of primary pulmonary vascular sclerosis, to be described later) some other cause for the circulatory symptoms was present. It may therefore be said that there is no clear evidence that pulmonary vascular sclerosis usually gives rise to symptoms.

The clinical picture as depicted in the literature is as follows:

Onset.—Often the patient has had chronic bronchitis or asthma for many years. Then congestive heart failure characterized by dyspnea, cyanosis, edema and other symptoms, gradually appears and steadily progresses. In these cases the sclerosis is secondary to chronic pulmonary disease. In other cases either dyspnea or cyanosis is the first symptom, followed by other symptoms of congestive heart failure. In most of these cases the sclerosis is secondary to mitral stenosis. In three casesⁿ the onset was after childbirth and the first symptom was edema of the legs.

Dyspnea.—Dyspnea, often severe and associated with orthopnea, was present in most of the cases reported. In some cases^o dyspnea was slight or absent, and the authors said that dyspnea was strikingly slight as compared with the cyanosis—a statement that is not borne out by most of the published case reports. Some authors have attributed the dyspnea directly to the arterial lesions and have said that narrowing of the arteries causes a more rapid flow of blood through the lungs and therefore insufficient oxygenation of the blood, resulting in dyspnea. But oxygenation occurs in the capillaries, and narrowing of the arteries does not necessarily cause quickening of the flow through the capillaries. In any case the weight of the evidence favors the view that a reduction in the vital capacity is the chief cause of dyspnea, and it is difficult to see how the arterial changes could directly cause a diminution in the vital capacity.

(n) 47, 102, 262.

(o) 103, 106, 186, 239, 262.

Cyanosis.—Cyanosis as intense as that in cases of congenital cardiac disease is usually said to be an early symptom, though in some of the cases^p reported it was slight or absent. Thomas²⁹⁵ said that cyanosis does not occur until the roentgenogram shows evidence of pulmonary vascular hypertension (bulging of the pulmonary artery and of the conus of the right ventricle) and is usually not marked until venous stasis is superadded. Cyanosis has been attributed to narrowing of the pulmonary arteries and a consequently more rapid flow through the capillaries, but there is no reason that narrowing of the arteries should quicken the flow through the capillaries. Cyanosis has also been attributed to a diminution in the number of capillaries as a result of emphysema, pulmonary fibrosis and other conditions, with a reduction in the volume of oxygenated blood. A sufficient reduction in the number of capillaries may indeed reduce the flow of blood through the lungs and therefore the volume of blood oxygenated per minute, but if all else is normal, all the blood that flows through the lungs and reaches the systemic circulation would be fully oxygenated, so that cyanosis should not occur. The cyanosis is probably due to the fact that some blood flows through the lung tissue that is inaccessible to air because of fibrosis, edema, etc., so that it remains unoxygenated. It is unlikely that pulmonary vascular sclerosis per se has any influence.

Hemoptysis.—This was sometimes a prominent symptom, especially in cases of mitral stenosis, pulmonary tuberculosis and other chronic pulmonary infections. Infarcts were sometimes present. Pulmonary vascular sclerosis, though it has often been blamed, does not seem to be responsible.

Pain.—Pain of a pleural type may occur in cases of pulmonary infection or of pulmonary infarction. In addition, so-called hypercyanotic angina, or dyspragia intermittens angiosclerotica pulmonalis, has been described.^q Posselt²³⁹ said that Nothnagel observed pain in 18 per cent of cases of mitral stenosis. The attacks are produced by exertion or excitement. There is retrosternal pain radiating into the depths of the lungs and associated with an intensification of the cyanosis and sometimes with restlessness and anxiety. The pain is sometimes relieved by deep breathing. Posselt suggested that spasm of the small pulmonary vessels causes, in some unspecified way, an increase in the cyanosis and also a raised pressure in the pulmonary vessels, which stretches the sclerotic large arteries and so causes pain. This theory is entirely speculative. More probably the pain is a variety of ordinary angina. The cyanosis is associated with anoxemia of the myocardium as well as of other tissues, and perhaps during exertion this may increase

(p) 47, 174, 246, 262.

(q) 96, 239, 276, 288, 295, 304.

to the point at which pain is produced. Though many authors have said that hypercyanotic angina may occur, only a few cases have actually been described. The only case in the present series occurred in a boy of 11 with primary pulmonary vascular sclerosis and will be discussed in the appropriate section.

Mental Symptoms.—These occur occasionally, especially when there is intense cyanosis. The patient becomes increasingly drowsy and may fall asleep even while eating. Finally he relapses into a coma and dies. Loss of weight sometimes occurs, as in other forms of chronic cardiac disease, but it is not a leading symptom.

Clubbing of the Fingers.—This sometimes develops, especially in cases of chronic pulmonary disease, and possibly is to be attributed to this and the chronic cyanosis rather than to the pulmonary vascular sclerosis.

Physical Signs in the Lungs.—There may be the signs of disease of the lungs to which the sclerosis is secondary (such as emphysema, pulmonary fibrosis, bronchiectasis and tuberculosis). There may also be crepitations at the bases, signs of pleural effusion and other signs as a result of congestive heart failure. Ulrich³⁰² also described palpable pulsation of the intercostal spaces due to systolic pulsation of the lungs as a result of the high pressure in the pulmonary vessels.

Cardiac Physical Signs.—Signs of cardiac disease to which the pulmonary vascular sclerosis is secondary may be present. Posselt²³⁹ said that in cases of mitral stenosis with pulmonary vascular sclerosis the apical diastolic thrill tends to spread up the left sternal border and that sometimes there is a fine thrill at the pulmonary area which is increased by exertion and leaning forward. Dulness and tenderness are noted on percussion over the dilated pulmonary artery in the second and third spaces on the left side. There are a pulmonary systolic murmur transmitted to the left and an accentuated pulmonary second sound sometimes followed by a diastolic murmur, which is due not to functional incompetence of the pulmonary valve, as most persons think, but to the propagation upward of the mitral diastolic murmur. No one but Posselt has ever succeeded in eliciting these signs.

In the absence of mitral stenosis there are often no abnormal cardiac physical signs, though often the heart is enlarged to the right or to both the right and the left and the pulmonary second sound is accentuated. Occasionally there is a gallop rhythm on the right side, best heard near the lower end of the sternum.

Signs of Congestive Heart Failure.—Engorgement of the cervical veins, enlargement of the liver and edema were usually present before death in the cases that have been reported.

Polycythemia.—This is often present in cases of cyanosis, the highest recorded count being 9,430,000 erythrocytes, but it is not constant and there may be anemia.

Roentgenographic Observations.—The left middle arc of the shadow of the heart is formed by the pulmonary artery and the conus of the right ventricle. In the right anterior oblique view the middle of the three impressions on the barium-filled aorta is formed by the pulmonary artery.²²⁵ The hilar shadows, according to Laubry,¹⁵⁹ are formed by the right and left pulmonary arteries. The pulmonary veins are normally invisible. In cases of hypertension of the pulmonary vessels the left middle arc is more prominent and longer and the hilar shadows are enlarged and pulsate more than normally, especially in cases in which there is incompetence of the pulmonary valves.²³⁴ Ulrich³⁰⁴ also described a "diaphragmatic dance," an up and down movement of the diaphragm that was synchronous with the heart beat. At this stage there may not be any symptoms, or there may be slight dyspnea and cyanosis on exertion. When heart failure occurs the hilar shadows become still wider and of uneven density and show indistinct edges. The lungs, especially centrally, are less transparent. This "syndrome of venous stasis" may be dissipated by treatment for heart failure, but the signs of the underlying pulmonary vascular hypertension persist. Sclerosis of the pulmonary artery rarely shows roentgenographically, as calcification is rare, but it is said that when there is marked sclerosis the pulsation of the left middle arc is diminished. Moniz²⁰⁹ injected intra vitam from 6 to 8 cc. of a 120 per cent solution of sodium iodide directly into the right auricle by means of a long catheter introduced through a vein at the elbow. The pulmonary vessels were thus made radio-opaque and were visible in roentgenograms made directly after the injection. It is improbable that the information to be gained in this way can justify the risk to which the patient is exposed.

The electrocardiogram, in the few cases in which it was recorded, showed a preponderance of the right ventricle, sometimes with negative T waves in leads 2 and 3. Daly⁶⁸ showed in the dog that obstruction of the pulmonary artery causes the T wave in lead 3 to become more negative.

Course.—The course is usually said to be steadily downward, with progressive heart failure which is uninfluenced by treatment. However, many cases have been described in which temporary improvement occurred. Death is usually due to heart failure but occasionally to intercurrent infection. The duration of symptoms varies from a few months to forty-four years. Usually the patient dies within two years of the appearance of symptoms of heart failure.

ANALYSIS OF CASES

The cases in the present series have been analyzed to show the relationship of the secondary pulmonary vascular sclerosis to the clinical symptoms, as recorded in the case reports.

1. *Congestive Heart Failure*.—This was present in 25 of the 100 cases (fig. 17 and table 23). In 5 the right ventricle was normally thick, in 14 (56 per cent) moderately thick and in 6 (24 per cent) greatly thickened. Figure 17 shows that in all divisions of the pulmonary vascular bed the sclerosis was greater than it was in the 75 patients without heart failure, but it should be remembered that this group of 75 included a greater proportion of persons under 40. In each of the divisions of the pulmonary vascular bed greater sclerosis than in the cases of heart failure occurred in some one of the etiologic groups. Since greater sclerosis was often present without heart failure, it may be concluded that although the conditions causing heart failure also

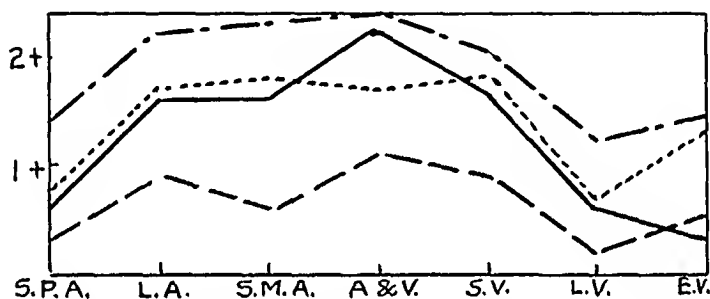


Fig. 19.—Graph showing the relationship of the degree of cyanosis to the degree of sclerosis found throughout the pulmonary vascular bed. The dot-and-dash line represents all the patients with cyanosis, the dotted line, all the patients without cyanosis.

favor the development of pulmonary vascular sclerosis, the sclerosis is not responsible for the symptoms of heart failure.

2. *Cyanosis* (table 27 and fig. 19).—Cyanosis was present in 17 cases. In 4 the right ventricle was normal, in 9 moderately thickened and in 4 greatly thickened. The average degree of sclerosis was greater than in the "no cause" group, but in each division of the pulmonary vascular bed the sclerosis was greater in some one of the etiologic groups. Moreover, the degree of sclerosis was only slightly less in the 83 patients without cyanosis. Thus, though cyanosis is often associated with marked pulmonary vascular sclerosis, the relationship cannot be direct since more marked sclerosis may occur without cyanosis.

3. *Polycythemia*.—The blood count was recorded in 47 cases. It was regarded as normal if it was between 4,500,000 and 5,000,000 and

TABLE 27.—*Relationship of Cyanosis to the Degree of Sclerosis Throughout the Pulmonary Vascular Bed*

Patients with Cyanosis	Sclerosis										Blood Count						
	Stem of Pulmonary Artery		Large Elastic Arteries		Small Muscular Arteries		Arterioles and Venules		Small Veins				Large Veins		Extrapulmonary Veins		
	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis			No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	
17	11	1.4+	16	2.2+	17	2.3+	15	2.4+	15	2.0+	11	1.2+	9	1.4+	9	3.5%	67%
	65%		94%		100%		88%		88%		65%			67%			
	No. with Sclerosis		Degree of Sclerosis		No. with Sclerosis		Degree of Sclerosis		No. with Sclerosis		Degree of Sclerosis		No. with Sclerosis		Degree of Sclerosis		
	Extrapulmonary Veins		Large Veins		Muscularity of Veins		Thickness of Right Ventricle		Low		Normal		High		Cyanosis		
	Little		Excessive		Normal		Moderately Thickened		Greatly Thickened		Normal		Low		Normal		
	35%		55%		24%		58%		20%		67%		28%		25%		

TABLE 28.—*Relationship of the Blood Count to Sclerosis Throughout the Pulmonary Vascular Bed*

Blood Count	No. of Patients	Sclerosis										Muscularity of Large Veins			Thickness of Right Ventricle										
		Stem of Pulmonary Artery		Large Elastic Arteries		Small Muscular Arteries		Arterioles and Venules		Small Veins		Large Veins		Extrapulmonary Veins		Normal	Moderately Thickened	Greatly Thickened							
		No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis										
Low (under 4.5×10^6)	27	13 1 lost 50%	0.8+	26 93%	1.8+	25 92%	2.1+	25 92%	2.3+	25 92%	2.5+	17 63%	1.4+	16 lost 59%	6	1.5+	14 52%	6 22%	7 26%	13 48%	10 37%	4 15%	3 15%	1 3%	1 3%
Normal (4.5 to 5.5×10^6)	13	8 1 lost 67%	1.1+	13 100%	1.8+	11 85%	1.9+	12 92%	2.2+	12 92%	1.8+	5 1 lost 32%	0.6+	4 8 lost 50%	2 17%	7 58%	3 23%	3 23%	3 23%	8 67%	3 23%	1 8%	3 23%	1 8%	3 23%
High (over 5.5×10^6)	7	4 57%	1.3+	6 1 lost 100%	2.2+	7 100%	1.4+	7 100%	2.7+	7 100%	2.0+	2 3 lost 50%	0.5+	1 6 lost	2 30%	2 90%	3 43%	1 20%	2 30%	3 43%	4 57%	0	0	1 14%	1 14%

low and high if below or above these limits, respectively. Table 28 and figure 20 show that no relationship could be traced between the blood count, the thickness of the right ventricle and the presence of cyanosis or sclerosis of the pulmonary vessels.

4. *Hypercyanotic Angina*.—This occurred only in the boy with primary pulmonary vascular sclerosis and will be discussed under that heading.

5. *Hemoptysis* (table 29).—This occurred in 9 cases, in 5 of which the right ventricle was thickened. The average degree of sclerosis was somewhat greater in all divisions of the pulmonary vascular bed than in the "no cause" group but was less in each division of the pulmonary vascular bed than in some of the etiologic groups. Thus, though the factors which cause hemoptysis also favor the development of pulmo-

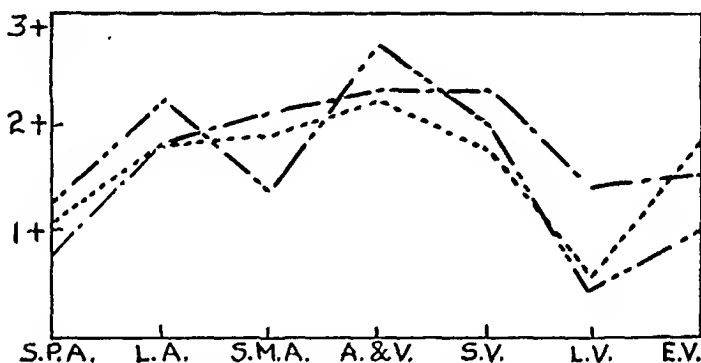


Fig. 20.—Graph showing the relationship of the blood count to the degree of sclerosis found throughout the pulmonary vascular bed. The dot-and-dash line represents patients with a low blood count; the dotted line, the patients with a normal blood count, and the two-dots-and-dash line, the patients with a high blood count.

nary vascular sclerosis, there is no reason to believe that there is any direct relationship between the two.

6. *Electrocardiography*.—In 12 cases (table 30) electrocardiograms were made. In the 3 patients with normal electrocardiograms there was fairly marked sclerosis, though less than in those with abnormal electrocardiograms. It is interesting to note that the right ventricle was greatly thickened in all 4 patients with left axis deviation, in 1 of the 3 with normal tracings and in 1 of the 4 with intraventricular block (in the remaining 3 of these it was moderately thickened). The electrocardiogram, therefore, gives no information as to the state of the pulmonary vascular bed.

TABLE 29.—*Relation of Hemoptysis to the Degree of Sclerosis Throughout the Pulmonary Vascular Bed*

No. of Patients		Sclerosis												Muscularity of Large Veins				Thickness of Right Ventricle							
		Stem of Pulmonary Artery		Large Arteries		Small Muscular Arteries		Arterioles and Venules		Small Veins		Large Veins		Extrapulmonary Pulmonary Veins		Muscularity of Large Veins		Normal		Moderate		Excessive		Cyanosis	
9	1 lost 89%	7	1.5+	6	1.9+	6	2.1+	9	2.2+	8	2.3+	5	1.4+	3	1.8+	1	3	4	3	2	3	2	3	3	3
		No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	Little	Moderate	Excessive	Normal	Moderate	Excessive				
		lost 89%		100%		100%		100%		89%		1 lost 63%			lost 75%		13%	37%	44%	33%	22%				33%

TABLE 30.—Relation of the Electrocardiographic Observations to the Degree of Sclerosis Throughout the Pulmonary Vascular Bed

	No. of Patients	Sclerosis												Muscularity of Large Veins			Thickness of Right Ventricle											
		Stem of Pulmonary Artery		Large Arteries		Small Arteries		Arterioles and Venules		Small Veins		Large Veins								Extrapulmonary Pulmonary Veins								
		No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	No. with Sclerosis	Degree of Sclerosis	Little	Moderate	Excessive	Normal	Moderate	Excessive	Cyanosis				
Electrocardiographic Observation																												
Normal	3	2	0.7+	3	2.0+	3	1.7+	3	1.7+	3	2.0+	3	1.7+	3	2.0+	3	2.0+	1 lost	0	1	0	2.0+	0	1	1	1	1	1
Right axis deviation	1	1		1		0		0		0		0		0		0		1 lost	0	1	0	2.0+	0	1	1	1	1	1
Left axis deviation	4	1	2.0+	4	2.0+	4	2.8+	4	2.8+	4	2.8+	2	1.0+	1 lost	2	1.0+	2	1	0	0	0	4	4	4	1
Intraventricular block	4	3	1.3+	4	2.5+	4	2.3+	4	2.3+	4	2.8+	3	1.5+	3	1.5+	3	1.5+	3 lost	1	2	0	0	0	3	1	1	1	2

SUMMARY

Thus, sclerosis in the vessels of the pulmonary circulation is almost constantly found at autopsy, though often it is only slight. It is as common as systemic vascular sclerosis, though usually not so severe. This robs pulmonary vascular sclerosis of much of the significance that has been attached to it. Like systemic vascular sclerosis it may exist without producing any obvious harmful results. Indeed, it is much less dangerous than systemic arteriosclerosis, since it is much more difficult to cause infarction of the lungs by occluding its vessels than in organs such as the heart or brain. If infarcts are produced, the rest of the lung is easily able to take over the function of the portions destroyed, so that disastrous consequences, such as those of infarction of the brain or heart, are not produced. Harmful results of pulmonary vascular sclerosis may be expected to follow only if the sclerosis so obstructs the pulmonary circulation as to embarrass the right ventricle. It is known that the most extreme systemic vascular sclerosis may occur without a rise in the systemic blood pressure or any embarrassment of the left ventricle, though with great aortic atheroma, owing to loss of elasticity of the aorta, the systolic pressure may be slightly raised and the diastolic pressure slightly lowered. It has been suggested that this may also occur in cases of sclerosis of the large pulmonary arteries, but if it does, it is not likely to embarrass the right ventricle seriously.

The present investigation shows that in the majority of cases of even severe pulmonary vascular sclerosis there are no circulatory symptoms, and that in 24 of the 25 patients with circulatory symptoms there was present some disease of the heart or lungs which could adequately account for the circulatory symptoms, even in the absence of pulmonary vascular sclerosis. The exception was an example of the unusual condition of primary sclerosis and will be discussed in the next section. It may therefore be concluded that pulmonary vascular sclerosis is common but only rarely of clinical importance.

(To be concluded)

PULMONARY ABSCESS AND PULMONARY GANGRENE

ANALYSIS OF NINETY CASES OBSERVED IN TEN YEARS

B. S. KLINE, M.D.*

AND

S. S. BERGER, M.D.†

CLEVELAND

In the past ten years at Mount Sinai Hospital (two hundred and seventy beds), fifty-five cases of pulmonary spirochetosis, better designated Miller-Vincent's infection of the lung, including thirty-nine cases of pulmonary gangrene, have been observed, as well as twelve cases of bronchogenic pulmonary abscess and twenty-three cases of embolic pulmonary abscesses.

The embolic pulmonary abscesses were associated with areas of suppuration elsewhere in the body and were manifestations of generalized pyemia or bacteremia.

Of the local bronchogenic pulmonary lesions, gangrene was observed more than three times as frequently as abscess. Although all the cases presented clinically the picture of so-called typical abscess of the lung, they were usually readily recognized by distinguishing characteristics as cases of gangrene and abscess, respectively. Of the thirty-nine cases of gangrene, thirty-two were in adults and seven in children. Of the twelve cases of bronchogenic abscess eight were in children and four in adults. Twenty-two cases of pulmonary gangrene followed an operation, which in all but a few instances was performed under general anesthesia. Half the operations were on the oral cavity. This incidence emphasizes the danger of aspiration of infective material from the oral cavity, especially during general anesthesia.

Ninety-six per cent of the patients with embolic pulmonary abscess died. The mortality in cases of bronchogenic abscess was 58 per cent. In contrast to these results are those in the cases of properly treated patients with pulmonary gangrene with cavitation, a much more severe process than pyogenic abscess. In twenty-five such cases, mortality was only 32 per cent. Mortality in the whole group of cases of gangrene, including fourteen in which there was no treatment with arsenic

* Chief of the Laboratories.

† Chief of the Department of Medicine.

or only one treatment when the patient was practically moribund (within four days of death), was 49 per cent.

Although at times it is a problem clinically and anatomically to distinguish abscess, putrid abscess and early gangrene with the organisms both of suppuration and of gangrene present, this difficulty does not justify the consideration of pulmonary gangrene and abscess of the lung as one entity. Pyogenic organisms never produce gangrene, whereas the fully developed and characteristic lesion produced by spirochetes, fusiform bacilli and vibrios is not abscess, but gangrene.

The sputum in the cases of pulmonary gangrene was foul-smelling, grayish brown or grayish green and occasionally blood-streaked or bloody, and, when washed free of oral mucus, it was found to contain characteristic oral spirochetes, fusiform bacilli and vibrios (the Miller-Vincent organisms).¹ In the cases of abscess, on the other hand, the sputum was whitish yellow, mucopurulent or purulent, without appreciable odor, and contained pyogenic organisms, usually staphylococci.

In the cases of bronchogenic abscess, at autopsy the lesion was usually found limited to one lobe (to a lower lobe most frequently), was not infrequently multiple and was at times confluent and associated with a regional pneumonia, but not with pyemia or bacteremia. The abscesses varied in size, were reddish gray or grayish yellow and did not have an appreciable odor. In a few cases in the early stage, the lesions were reddish. Smears and cultures showed staphylococci in all the cases. Sections of early lesions stained by the Gram method showed numerous clusters of staphylococci in the bronchial branches and in the alveoli, whereas the regional blood vessels were not involved.

In the cases of gangrene, on the other hand, the fully developed characteristic lesion was ragged, penetratingly foul-smelling, and brownish or greenish, and smears and sections from it showed innumerable spirochetes, fusiform bacilli and vibrios (Miller-Vincent's organisms). As in bronchogenic abscess, gangrene was limited usually to one lobe, most frequently to a lower lobe. At times, however, more than one lobe was involved in the process.

As not more than several hundred cases of pulmonary spirochetosis have thus far been reported in the United States (one hundred and eighteen cases collected by Smith up to November 1927²), it is probable that many cases diagnosed as instances of pulmonary abscess from clinical and roentgenologic evidence, but not supplemented by a study

1. Kline, B. S., and Berger, S. S.: The Relation of Oral Spirochetosis to Pulmonary Gangrene, *J. Am. Dent. A.* **15**:64, 1928.

2. Smith, D. T.: Fuso-Spirochaetal Disease of the Lungs: Its Bacteriology, Pathology and Experimental Reproduction, *Am. Rev. Tuberc.* **16**:584, 1927; *Oral Spirochetes and Related Organisms in Fuso-Spirochaetal Disease*, Baltimore, Williams & Wilkins Company, 1932.

of the sputum as we have outlined, were, in reality, cases of pulmonary gangrene.

In addition to the thirty-nine cases of fully developed pulmonary gangrene with sputum containing the Miller-Vincent organisms, there were six cases of pneumonitis and eight cases in which the involvement was limited to the bronchi, some patients having associated bronchiectasis, in which the sputum contained these organisms. In the majority of the cases of pulmonary gangrene observed clinically, the pleura was involved, frequently so severely as to require thoracostomy; in two cases, following repeated thoracentesis, gangrenous cellulitis of the wall of the chest developed (thoracentesis in these cases is now considered contraindicated unless it is to be followed promptly by resection of the ribs and pleural drainage in the traumatized area). Among the cases of Miller-Vincent's infection were two in which the lesion was apparently limited to the pleura. One case of this series was associated with active pulmonary tuberculosis.

Arsphenamine therapy was particularly efficacious in the cases of pneumonitis with sputum containing Miller-Vincent's organisms. The most striking results, however, were obtained in the cases of frank gangrene. Seventeen of twenty-five seriously ill patients who were intensively treated with arsphenamine recovered. Large or maximum doses were given every two or three days as a routine, except in some of the earlier cases.³ The favorable results in gangrene are in marked contrast to only five recoveries in twelve cases of bronchogenic abscess, a less severe process.

In addition to arsenical therapy the patients with Miller-Vincent's infection received treatments indicated by the symptoms and general condition. Toxemia, general debilitation, insomnia, excessive cough, hemorrhage and anemia were combated with the usual therapeutic measures. In general, transfusions, a diet high in calories, inhalations of oxygen and supportive measures of all kinds were employed. Postural drainage was used as a routine, as in the treatment of abscess, and should never be neglected. Bronchoscopic drainage was found useful in the early stages of cavitation.

In several cases of pulmonary gangrene phrenicectomy or phrenicotomy was done on the involved side. Artificial pneumothorax may be employed; the indications are the same as for lesions other than Miller-Vincent's infection. The lesion must be far enough from the periphery of the lung that rupture and empyema will not occur. It is well to bear in mind that by compression of the lung anaerobic conditions are favored and that a flare-up of the infection may follow. Likewise,

3. Kline, B. S., and Berger, S. S.: Spirochetal Pulmonary Gangrene Treated with Arsphenamins, *J. A. M. A.* 85:1452 (Nov. 7) 1925.

drainage from the compressed area may be hindered. Phrenicectomy may be employed for basal lesions, but the contraindications are the same as for artificial pneumothorax. These measures are more suitable for the treatment of abscess than for that of gangrene. When phrenicectomy or artificial pneumothorax is employed chiefly, arsenic therapy should be continued. The open operation is preferable whenever it can be safely employed.

Wassermann tests and slide precipitation tests for syphilis in cases of pulmonary spirochetosis (Miller-Vincent's pneumonitis, gangrene, bronchitis, pleuritis) gave positive results only in cases of syphilis in addition to the nonsyphilitic pulmonary lesion. A few uncomplicated cases gave doubtful results in the Wassermann or slide tests.

The spirochetes, fusiform bacilli and vibrios (Miller-Vincent's organisms) of pulmonary gangrene are identical with those present in

TABLE 1.—*Incidence of Postoperative Pulmonary Complication in Persons Treated and Not Treated*

	Service Patients Treated				Private Patients Not Treated			
	Surgical Operations	Pulmonary Complications	Percentage	Fatalities	Surgical Operations	Pulmonary Complications	Percentage	Fatalities
1928.....	1,024	1	0.097	0	2,261	16	0.7	4
1929.....	1,294	4	0.31	1	2,520	14	0.55	4
1930.....	1,296	2	0.15	1	1,945	19	0.97	8
1931.....	1,464	2	0.13	0	2,171	11	0.5	2
Total.....	5,078	9		2	8,897	60		18
Average.....			0.17				0.68	

the mouth in practically all adults (in the interproximal spaces between the gums and teeth). The lesion perhaps most frequently produced by these organisms is gingivitis. When observed early, the gums are somewhat swollen and injected and bleed readily on pressure. The commonest sites are adjacent to the rear molars. Overlying the swollen gums is usually a yellowish-white exudate which contains the characteristic spirochetes, fusiform bacilli and vibrios in large number. This lesion, although frequently overlooked by the patient and by the physician, is a menace to health, since from it the organisms may be aspirated into the lung and so produce gangrene.

For the past six years, under the direction of Dr. M. B. Galvin, the dental service of Mount Sinai Hospital has given preoperative oral therapy to patients in the public wards. Table 1 shows the incidence of postoperative pulmonary complication in persons treated and in those not treated from 1928 to 1931 inclusive. The results give evidence that pulmonary infections, including those by the Miller-Vincent organisms, may be prevented by proper oral hygienic or therapeutic measures.

CLINICAL OBSERVATIONS AND PATHOLOGY

PULMONARY ABSCESS

Embolic Pulmonary Abscess.—In the series reported here there were twenty-three cases of staphylococcic bacteremia or pyemia with embolic pulmonary abscesses. Of these, fourteen were in infants or children, and nine were in adults. One patient recovered, and twenty-two died. In sixteen cases a postmortem examination was made.

The embolic abscesses involved a number of lobes, were multiple and relatively small and were associated with areas of suppuration elsewhere in the body, representing a manifestation of pyemia or bacteremia. The clinical evidences of pulmonary involvement in the acute cases were not particularly striking and were masked by the symptoms of general sepsis. The high mortality and the high incidence of the condition in infants and children are noteworthy.

The embolic abscesses observed at autopsy in this series were multiple, usually small (from 5 to 15 mm. in diameter) and more or less spherical, occurring in a number of lobes and associated with areas of suppuration elsewhere in the body (in the kidneys, in the myocardium and occasionally in the brain). The lesions were grayish or yellowish and soft or viscid, with little or no odor. In a few cases in which the lesions were numerous, they were coalescent in places. Early lesions were reddish and more coherent. In some cases there were infarction and suppuration, with the lesions more or less wedge-shaped, larger than embolic abscesses and situated along the lower borders of the lobes. A number reached and involved the pleura. Smears and cultures showed the pyogenic organisms. In sections stained by the Gram method, abundant organisms were observed in and about occluded blood vessels. The involved pulmonary tissues were necrotic and usually completely replaced by pus.

Bronchogenic Pulmonary Abscess.—In the second group in this series, that of bronchogenic pulmonary abscess, there were twelve cases. Ten patients were male and two were female; there were eight infants and children and four adults. There was complicating bronchitis or pneumonia in eight cases. The condition developed following operation under general anesthesia in three cases and following operation under local anesthesia in one. The location of the lesions is indicated in table 2.

This type of abscess is aspiratory and, like embolic abscess, occurs most frequently in infants and children. It is usually limited to one lobe, a lower lobe most frequently. There may be multiple abscesses, however, and these at times are confluent. The abscess or abscesses are associated with regional pneumonia. A bronchogenic abscess is not associated with pyemia or bacteremia. In eight of the twelve cases in

the series there was no relation to a surgical procedure. The abscesses varied in size; the sputum did not have an appreciable odor, and the smears and cultures showed staphylococci in all cases. In one patient it was associated with an infection caused by *Bacillus pyocyaneus*. Five of the twelve patients recovered. The symptoms are those of pneumonia, which the abscess complicates; however, resolution fails to take place. In its stead, when the abscess begins to break down, abundant purulent material, at times blood-streaked, is expectorated. The odor, when present, is not distinctive and is never foul as in gangrene. Evidence of clubbing of the fingers may be present, appearing at times with surprising rapidity.

Signs of a cavity can be elicited both by physical and by roentgen examination as early as eight or ten days after the onset of symptoms. The spontaneous evacuation of the abscess through the bronchus may take place promptly and healing begin. This occurred in five of the twelve cases. When the lesion is progressive and a large area of suppuration appears the symptoms of toxemia with high fever, leukocytosis and progressive exhaustion develop, and death frequently results. This occurred in seven of twelve cases (mortality, 58.3 per cent) in spite of supportive measures, including postural and bronchoscopic drainage. It should be noted that the greater incidence of bronchogenic abscess in children probably depends on the fact that the oral flora at this time contains more staphylococci than later in life and that before 10 years of age children ordinarily do not harbor in their mouths appreciable numbers of spirochetes, fusiform bacilli and vibrios.

In contrast to the postmortem picture in embolic abscesses, the suppuration in cases of bronchogenic abscess was found limited to the lung only. Multiple lesions were occasionally found, but the process was usually limited to one or a few foci in one lobe. The lower lobes were most frequently involved. The lesions in general were larger than embolic abscesses and associated with areas of bronchopneumonia.

The local lesion was usually several centimeters or more in size, irregular in shape, at times owing to the coalescence of foci, and surrounded by inflamed lung tissue. The involved area was soft or viscid, gray, yellow or yellow-brown, with little or no odor unless the organisms of gangrene were present. Early lesions were reddish and hardly distinguishable from areas of pneumonia. Smears and cultures showed the pyogenic organisms, usually staphylococci, together with other oral cocci. In one case colon bacilli were present. In another *B. pyocyaneus* was also present.

Sections of early lesions stained by the Gram method showed numerous clusters of staphylococci in the bronchial branches and alveoli,

whereas the regional blood vessels were uninvolved. A case with characteristic findings is reported:

S. L., aged 6 months, was admitted to the hospital with signs of an incarcerated inguinal hernia on the right side. The patient was acutely ill, with a temperature of 102 F. She was operated on under local anesthesia. On the following day, the temperature rose to 105.5 F., the pulse rate ranged between 160 and 200 and the respiratory rate was between 60 and 80. Fine crepitant râles and dulness were present over the base of the chest on the left, and high-pitched distant tubular breath sounds were heard. There was marked abdominal distention. Three days after the operation the patient died. Autopsy revealed bronchopneumonia with a small abscess in the upper lobe of the left lung, fibrinopurulent pleurisy and local peritonitis.

PULMONARY SPIROCHETOSIS

The invasion of the pulmonary tissues by Miller-Vincent's organisms may induce bronchitis, pneumonitis, gangrene, pleurisy or a combination of these. The organisms concerned are generally present in the mouth of persons over 10 years of age, between the gums and the teeth and occasionally in the sinuses and the nasopharynx. Not infrequently, when local conditions permit, they multiply enormously and cause from mild to severe inflammation and gangrenous ulceration. Patients and physicians are frequently unaware of mild lesions which may be teeming with these organisms, free on the surface in the upper respiratory tract. Gingivitis containing these organisms about the rear molars is especially common.

The penetration of the lungs by organisms is favored when the cough reflex is abolished, as when the patient is under a general anesthetic or during deep sleep. Occasionally, infected food or other particles are accidentally aspirated into the trachea during full consciousness and cannot be coughed out.

Between the time of aspiration of the infected material and the onset of symptoms several days usually elapse. However, symptoms may be apparent within two days or may not appear until fourteen days later. The relationship between aspiration and the onset of symptoms may be definitely timed in those cases which occur following operation under general anesthesia. The infected material is aspirated into the lung during the period of anesthesia, and the resulting lesions depend on the amount of aspirated material, the number and virulence of the invading organisms and the local and general resistance of the patient. Symptoms and physical signs resulting from invasion of the pulmonary tract may appear within forty-eight hours or even earlier.

In those instances in which symptoms first appear several weeks after operation, it is probable that the aspiration of the infected material occurred within fourteen days prior to the onset of symptoms and is without any relation to the operation, as in those cases in which the

condition arises apparently spontaneously when no operation under general anesthesia has been performed. The symptoms in cases of Miller-Vincent's infection of the lungs also vary depending on whether the infection is primary or whether it is superimposed on some other condition.

The fifty-five cases of Miller-Vincent's infection of the lung were distributed as follows:

Type	No. of Cases
Gangrene	39
Pneumonitis	6
Bronchitis	8
Pleurisy	2

The age incidence was:

Age, Years	No. of Cases
3 to 9.....	4
10 to 19.....	3
20 to 29.....	12
30 to 39.....	11
40 to 49.....	12
50 to 59.....	6
60 to 69.....	7
	—
	55

It is noteworthy that the greatest number of cases (thirty-five of fifty-five, or 64 per cent) occurred in the age groups between 20 and 50 years. In contrast to abscess, which occurred twice as often in children as in adults, Miller-Vincent's infection of the lung occurred seven times as often in adults as in children (forty-eight adults, seven children).

In the majority of cases, there was moderate leukocytosis. The average white blood cell count in the fifty-five cases was 16,000. In one case (table 3, case 22) in which the disease progressed rapidly and resulted in death eleven days following the onset, there was granulocytopenia with the following white cell count:

Date	White Blood Cell Count
5/28	20,000
5/31	13,000
6/2	10,000
6/3	1,650
6/4	1,250
6/5	750
6/6	800
6/7	420
6/8	400
6/9	330
6/12	270

This fulminating case of acute gangrene of the lungs followed the extraction of a tooth and alveolectomy for gangrenous osteomyelitis under general anesthesia.

Anemia of the secondary type was observed in many cases and usually was not severe. Transfusion as a supportive measure was used with benefit.

In the acute Miller-Vincent's infection of the respiratory tract, fever is always present. In the parenchymatous pulmonary type the temperature may reach 105 F. In the chronic state, fever may be absent except during periods when the gangrenous purulent material is retained.

Cough is always present, with the same characteristics as are found in acute and chronic bronchitis, bronchiectasis and cavitation. The general symptoms depend on the stage of the involvement. In the acute stage the clinical process is indistinguishable from bronchitis, pneumonia or abscess. In the subacute stage it may resemble tuberculosis, bronchiectasis or abscess, and in the chronic stage the symptoms are those of a chronic suppurative disease of the lungs with the formation of cavities. The fetid character of the breath and of the foul sputum in all these conditions practically makes the diagnosis, and the presence of Miller-Vincent's organisms in the washed sputum establishes it.

Pulmonary Gangrene.—There were thirty-nine cases of pulmonary gangrene in this series (over three times the number of cases of bronchogenic abscess observed), thirty-two in adults and seven in children, twenty-five in males and fourteen in females. The youngest patient was 3 years of age, and the oldest, 69. Seventeen cases followed operation (eight oral, nine nonoral) under general anesthesia, four followed operation (two oral, two nonoral) under local anesthesia and seventeen had no relation to operation.

Pulmonary invasion in these cases was usually ushered in with fever and occasionally with chills, pain in the chest and cough and expectoration, symptoms which usually led to the diagnosis of pneumonia. At first, the physical signs and roentgen observations could not be differentiated from those of ordinary pneumonitis. The history and the character of the sputum, however, made possible the prompt diagnosis of Miller-Vincent's infection. The sputum, which at first may be mucopurulent and occasionally hemorrhagic and without appreciable odor, soon becomes abundant, thin, gray or brown-green, with an intensely foul odor, and microscopic examination reveals the characteristic oral spirochetes, fusiform bacilli and vibrios (Miller-Vincent's organisms).

Pulmonary gangrene and pulmonary abscess should not be confused with each other, for they are two distinct and well defined diseases.

Failure to recognize this may result in unnecessary loss of life, since pulmonary gangrene with characteristic etiology and pathology may be combated by specific therapy which is much more efficacious than are the measures for pulmonary abscess.

The process in the lung in gangrene is one of progressive ulceration in the pneumonic areas, resulting in the formation of cavities of which there may be one or more scattered throughout one or more lobes. The cavities vary in size and differ from tuberculous cavities in that they are free from trabeculations. In the former the process is more fulminating, and the destruction is complete. In this stage both the physical signs and roentgenograms readily reveal the presence of cavities. The characteristic fluid level or the fluid and air, which shift with a change in position, may readily be demonstrated. In some cases early detection depends on both physical and roentgen examination, especially following postural drainage.

In the early stages, before the communication with the bronchus is fully established, there may be only one evacuation of foul-smelling sputum from the area of cavitation containing the organisms, blood and necrotic lung tissue, and a number of days may elapse before communication is again established and similar sputum is brought up. The patient is always aware of having expectorated this foul-smelling material and when questioned invariably reveals it. If the communication between the cavity and the bronchus is intermittent, the sputum brought up at times fails to have the characteristic odor and is devoid of the characteristic Miller-Vincent organisms, in which case an early diagnosis is missed.

The expectoration of foul-smelling sputum in the presence of an unclean mouth, a history of a recent operation or a preexisting pulmonary condition, such as pneumonia, tuberculosis or a neoplasm, on which gangrene may be superimposed makes the diagnosis of pulmonary gangrene probable. In the more advanced stages of gangrene, the odor is so pronounced that entrance into the room is sufficient for a probable diagnosis, since both the sputum and the breath are sickeningly foul, and the odor completely permeates the room. Examination of the washed sputum and physical and roentgen examination readily reveal conclusive evidence of the Miller-Vincent infection.

In a few cases in the series the signs, symptoms and anatomic observations were those of pulmonary gangrene without appreciable pneumonitis or a preexisting pulmonary lesion. These were of a fulminating type, with a rapid course, speedily terminated by death. In the majority of the cases, however, the findings were those of gangrene and cavitation following pneumonitis. The course was a matter of weeks or months, reflecting a less severe process, and to the signs and symptoms of pneumonitis those of cavitation were promptly added.

Early in the fulminating, and later in the less severe, types, pneumonitis may be followed by complete resolution, but not infrequently the process becomes arrested only to become active again if treatment is discontinued. In some cases the process is slowly progressive. In the subacute and chronic types the development is more insidious and the systemic reaction less marked. The subacute and chronic types either result from primary spirochetosis or represent a secondary superimposed invasion on a previous lesion in the lung, such as old chronic bronchitis, bronchiectasis, tuberculosis or tumor of the lung. Subacute and chronic types may flare up into an acute process with gangrenous destruction of the tissues and assume all the aspects of the more acute, menacing lesion.

In one case the gangrenous process complicated active tuberculosis of the lungs. There was no apparent benefit following arsphenamine therapy, and the tuberculous process steadily progressed, causing death after several months.

It is of the utmost importance to make the diagnosis of pulmonary infection with the Miller-Vincent organisms as soon as possible, in order to prevent the extensive gangrenous ulcerative processes which these organisms produce. Antisyphilitic therapy with arsphenamine is most effective when begun early. Arsenic in the form of arsphenamine or neoarsphenamine, administered to the point of causing toxicity, is the most valuable single measure in the treatment of pulmonary gangrene.

In the acute stage, intensive treatment is necessary to prevent rapid gangrenous destruction. The arsphenamine should be administered intravenously in appropriate dosage, according to the age and weight of the patient, and should be given in full doses every other day or every third day until improvement is manifest. The temperature, pulse, toxemia and character of the sputum (diminution of the odor) are the guides. Later treatment should be administered every four days, with the physician alert for the onset of symptoms of arsenic poisoning, i. e., itching of the skin, gastro-intestinal upset, renal damage and jaundice. Treatment should be continued until all the symptoms of the infection have disappeared, the sputum has lost its odor and the physical signs have disappeared. Beside the physical signs, roentgen examination is helpful in depicting the course of the disease. It has been our experience that acute bronchitis, acute pneumonitis and even early gangrene with cavitation heal when energetic treatment is given. In most instances, arrest of the activity of the Miller-Vincent organisms can be accomplished if energetic treatment is begun promptly within one to two weeks after the onset of symptoms. When the spirochetal invasion is secondary, specific therapy will arrest only the process due to it, and the associated condition, such as tuberculosis, tumor or some other chronic pulmonary condition, may go on indefinitely.

In the acute stage, in addition to arsphenamine therapy, oxygen administered under pressure in a tent is advisable. It is needless to stress the fact that supportive measures of all kinds, hydrotherapy (especially when the temperature is high and toxemia is great) and control of excessive cough, assuring rest and sleep, are always indicated. In the subacute stage, as soon as the patient is able, postural drainage should be carried out. Bronchoscopic drainage in this stage is at times followed by prompt healing. If, in spite of these measures, cough, abundant sputum with odor, continued impairment of the general health and clubbing of the fingers develop, the more chronic stage with cavitation is established. If the acute gangrenous process results in the formation of cavities, and healing under intensive treatment has not taken place at the end of from four to six weeks, healing of the cavitation is unlikely to occur thereafter, and the chronic stage with the usual sequelae of the formation of cavities is established. This condition must be dealt with according to the general condition of the patient and the location and number of the cavities. When arsphenamine and postural and bronchoscopic drainage, with general supportive measures, fail to accomplish healing in from four to eight weeks after the onset, pneumothorax or phrenicectomy may be tried. The use of iodized poppy-seed oil 40 per cent is helpful in determining the location and the extent of the lesions and in indicating further therapy.

If no pleural adhesions are present, if the cavity is limited to one lobe and is not too near the periphery but near the hilus, artificial pneumothorax may be tried. Phrenicectomy may be tried when the lesion is not too near the periphery but is in the lower lobe near the diaphragm. When the condition does not yield to these measures, when the cavity is large or when there are several which may be intercommunicating, surrounded by a dense wall and infiltration, the more formidable surgical procedure of external drainage is necessary for the eradication of infection. This is the operation of choice. The cautery operation of Graham (which can be done in several stages to diminish the shock of a more extensive one-stage operation) may be successful in the hands of experienced surgeons. Lobectomy also has been successfully performed by some. These procedures, however, are more dangerous.

At autopsy, in contrast to the grayish or yellowish suppuration with little or no odor in cases of abscess, the lesions in cases of pulmonary gangrene were ragged, brownish or greenish and penetratingly foul-smelling.

Pulmonary gangrene, like bronchogenic abscess, was found most frequently in the lower lobes. Occasionally more than one lobe was found to be involved. In the majority of cases gangrene was found involving pneumonic areas. In the acute cases, however, in which countless oral

anaerobes had been aspirated into the lungs from lesions in the upper respiratory tract, there was little regional pneumonia.

Sections stained with hematoxylin and eosin, by the Levaditi method and, best of all, by the Warthin and Starry methods, showed that the gangrenous process begins in and about the smaller bronchial branches with the first characteristics those of bronchopneumonia, followed by necrosis of the exudate and of the fixed tissue. Following this, the lesion steadily enlarges, and ulceration occurs in the older areas of necrosis. The lesion now is fully developed and characteristic of gangrene, consisting of a ragged, penetratingly foul-smelling, brownish or greenish ulcerated area, with innumerable oral spirochetes, fusiform bacilli and vibrios present not only in the areas of necrosis, but also at the advancing periphery. In a short time there is coalescence of the ulcers, with the formation of definite cavities and since no tissues are spared in the progression of the gangrenous lesion, no large ridges or bridges of tissue ordinarily remain. In the cases with ulceration or frank cavity formation the contained material consists not only of necrotic lung tissue and exudate but of innumerable bacteria, including the Miller-Vincent organisms and ordinary aerobic oral bacteria.

In some cases gangrenous cavities showed evidence of partial healing, with granulation tissue in the wall. In one case in another series several healed cavities with intact epithelial lining were present, together with more recent gangrenous cavities, extensive pneumonitis and a terminal large area of gangrene of the brain, all active lesions containing the characteristic Miller-Vincent organisms.

In the cases of gangrene and in those of abscess of the lung the pleura was frequently involved, and not uncommonly there was gangrenous effusion or empyema.

Gangrene was found complicating active pulmonary tuberculosis in one case in this series and has been reported involving degenerating tumors of the lung.⁴

The following report is of a characteristic case:

N. M., a woman, aged 33, had a tonsillectomy under general anesthesia on Sept. 2, 1924. She apparently was making a good recovery until September 13, when she complained of pain in the right side and had a high temperature and cough. Seen on September 15 in consultation, she showed well marked signs of infiltration of the upper lobe of the right lung. The temperature was 104 F., and there was marked prostration. The odor of the sputum was intensely foul, and it greatly annoyed the patient. A diagnosis of gangrene of the lung was made. The washed sputum showed innumerable Miller-Vincent organisms. The roentgen examination, made on September 18, revealed marked density in the upper part of the chest on the right side, with a cavity about the size of a silver dollar in the infraclavicular area. Treatment with sulpharsphenamine was instituted. The patient

4. Seecof, David: Personal communication to the authors.

made an uneventful recovery, and at the end of four weeks was able to leave her bed. Seven months later roentgen examination failed to reveal any evidence of the cavity.

This report illustrates a case of pulmonary gangrene with the formation of a cavity with complete healing following arsphenamine therapy. The diagnosis was made promptly, and energetic treatment was instituted, to which the complete healing may be attributed.

Pneumonitis with the Miller-Vincent Organisms.—There were six cases in the series, four in men, and two in women: one following operation (nonoral) under general anesthesia, one following oral operation with no anesthetic, and four having no relation to surgical procedure. All the patients recovered quickly following specific therapy.

The signs and symptoms in these cases were essentially those of ordinary pneumonitis of one or two lobes. In some the picture suggested postinfluenzal pneumonia, and in some lobar pneumonia was the first impression. In one case the picture suggested pulmonary tuberculosis.

As shown in table 2, none of the patients with pneumonitis or bronchitis caused by Miller-Vincent's organisms died. One of the two patients in whom the lesion was limited to the pleura died, but post-mortem examination was not permitted. In a number of cases of pulmonary gangrene, however, autopsy showed areas of pneumonitis containing the Miller-Vincent organisms, and in all of the cases there was bronchial involvement of varying degree. Furthermore, in many of the cases there was involvement of the pleura, and not infrequently gangrenous effusion was present.

In the areas of pneumonitis in the cases of gangrene the picture was not unlike that of ordinary bronchopneumonia with some interstitial involvement. In portions of the involved lung in some cases the lesion was that of bronchopneumonia with degenerative and necrotic changes of the cells of the exudate and fixed tissue. This lesion resembles somewhat the necrotizing lesion in certain stages of exudative tuberculosis. Smears and sections from areas of intact and necrotizing pneumonitis showed the characteristic Miller-Vincent organisms, together with a variable number of ordinary aerobic oral bacteria. In portions of the pneumonic areas in some cases, organization of the exudate was observed. As stated earlier, six patients in the series showed lesions apparently of this nature, without definite ulceration detectable by clinical or roentgen examination.

Miller-Vincent's Infection of the Bronchi.—There were eight cases: seven in men and one in a woman. The symptoms were much like those in cases of bronchitis caused by other organisms, and they depended on whether the condition was acute or chronic or an exacer-

bation of a chronic infection. A few cases showed signs and symptoms of bronchiectasis. The distinguishing character of the infection was made clear by the sputum. This was markedly fetid and contained the characteristic Miller-Vincent organisms. In these cases pulmonary hemorrhages occurred frequently, and the condition could readily be mistaken for pulmonary tuberculosis, neoplasm or the like. The general well-being of the patient with little systemic reaction, however, helps in the differentiation. In one instance, there was polycythaemia vera with enlargement of the spleen.

Chronic bronchial and chronic parenchymatous infections with the Miller-Vincent organisms, including bronchopulmonary cavity, may be present for years. This infection may dominate the picture or it may be found merely in association with other bronchopulmonary conditions. These processes may exist for years and be considered chronic bronchitis, bronchiectasis or tuberculosis, and usually the Miller-Vincent infection is unrecognized until an acute exacerbation with gangrene or some intercurrent infection or complication such as a gangrenous lesion in the brain appears as the final stage. In these cases, acute exacerbations are likely to occur with serious destruction of bronchopulmonary tissues. At these times, there are cough and expectoration of foul-smelling sputum containing the characteristic organisms. This devastating process may be controlled by arsphenamine therapy.

The bronchial lesions observed in cases of gangrene coming to autopsy varied from simple mild inflammation of the mucous membrane to complete destruction of the bronchial wall. In portions showing the milder lesions the exudate in the lumen and in the wall showed nothing characteristic except the presence of the Miller-Vincent organisms. In the more advanced cases the ulceration of the mucosa and the destruction of elastic tissue and even cartilage are characteristic, and the Miller-Vincent organisms are numerous. In some cases, there was complete necrosis of portions of the bronchial wall, with similar involvement of the regional parenchymatous tissue. The cavity formed thereby was a bronchopulmonary rather than a true bronchiectatic cavity. Some of the involved bronchi showed definite evidence of variable dilatation, with small, irregularly distributed, recent or old ulcerations of the wall. Such lesions readily harbor the Miller-Vincent organisms and permit the formation of whole colonies, which compose the whitish and yellowish balls expectorated in cases of bronchitis and bronchiectasis. In the eight cases of bronchitis with the Miller-Vincent organisms the lesions were doubtless similar to those observed in cases of pulmonary gangrene.

Miller-Vincent's Infection of the Pleura.—The symptoms in cases of Miller-Vincent's infection of the pleura are essentially those of any pleuritis, the differential diagnosis being made after thoracentesis.

In many cases of both acute and chronic pulmonary gangrene the pleura became involved, this complication not infrequently eventuating in pyopneumothorax. More commonly, associated with the inflamed pleura, a gangrenous effusion was found. In some cases (the earlier ones in this series), thoracentesis was followed by gangrenous cellulitis of the wall of the chest. In one case, seen in consultation (S.S.B.), the gangrene of the wall of the chest extended not only over the chest but over the trunk and down to the thigh. Because of the danger of this complication, thoracentesis, if performed, should be followed promptly by resection of the ribs and free drainage of the pleural cavity, permitting free communication with the air. This procedure, with energetic specific treatment, has resulted favorably when the condition seemed hopeless.

In two cases in this series, both in men, gangrenous pleurisy was present without appreciable involvement of the lung. In one case this condition complicated pneumonia, which apparently was minimal, but from which the process extended to the pleura. In the second case the condition followed a gunshot wound of the chest. In both cases the process eventuated in pyopneumothorax and the patients became desperately ill. The pleural contents were exceedingly foul-smelling and contained the characteristic organisms, which permitted a prompt diagnosis. Energetic treatment was instituted, followed by thoracentesis; wide resection was done, and arsenic therapy begun immediately, but in one case the patient died before more than one injection could be given. In the second, following repeated doses of arsphenamine, the patient recovered.

As shown in table 2, in many of the cases of pulmonary gangrene there was involvement of the pleura, and not uncommonly gangrenous effusion was present. In the cases observed at autopsy the pleural involvement varied from simple inflammation with little exudate containing the characteristic organisms, to lesions showing considerable infiltration of the pleural surfaces and the presence in the pleural cavity of large quantities of foul-smelling, thin, brown fluid containing innumerable Miller-Vincent's organisms. In some cases in which there were circumscribed lesions, fibrinous and fibrinopurulent exudate was present, and in the more chronic cases considerable organization of exudate with adhesions was observed.

PROGNOSIS

In this series, 96 per cent of the patients with embolic pulmonary abscesses died. The mortality in cases of bronchogenic abscess was 58 per cent. In contrast to these results are those in properly treated cases of pulmonary gangrene with cavitation, a much more severe

process than pyogenic abscess. In twenty-five such cases the mortality was only 32 per cent. The mortality in the whole group of cases of gangrene, including fourteen in which no arsenic treatment or one treatment was given when the patient was moribund (within four days of death), was 49 per cent.

ORGANISMS OF MILLER-VINCENT'S INFECTION

The spirochetes, fusiform bacilli and vibrios of pulmonary infections are identical with those occurring in the mouth. The first careful description of the spirochetes present in the mouth between the gums and the teeth was that of Miller,⁵ in 1890. In addition to the small, slender *Spirochaeta dentium* described by Koch in 1877, he observed larger forms (apparently identical with *Spirochaeta vincenti* and *Treponema macrodentium*) associated with a comma bacillus (*Spirillum sputigenum*, identified by subsequent investigators as *Vibrio proteus*). The spirochetes are motile anaerobes from 4 to 15 microns long with from two to twenty irregular coils. In smears they are gram-negative. The vibrio is a motile aerobe with a number of flagellae, curved, gram-negative, from 2 to 5 microns long and about 1 micron thick. The fusiform bacillus, first described as an inhabitant of the mouth by Vincent⁶ in 1899, is an anaerobe, nonmotile, straight, spindle-shaped, pointed at the ends, somewhat variable in its absorption of Gram's stain (smaller forms are gram-positive, and large forms, gram-negative), from 3 to 10 microns long and about 0.5 micron thick.

Plaut,⁷ in 1894, and Vincent,⁸ in 1896, pointed out the relationship of these organisms to the angina that bears their names. Plaut ascribed the angina to the Miller organisms (oral spirochetes and vibrios), and Vincent, to a spirochete and the fusiform bacillus.

Since the observations of Plaut and Vincent, the three types of organism—oral spirochetes (Miller), vibrios (Miller) and fusiform bacilli (Vincent)—have been found present not only in angina but in ulcerative gingivitis, dental caries, noma, pulmonary gangrene, gangrenous balanitis and gangrenous vulvitis. The color in gangrene in all likelihood is due to hemorrhage and to alteration of the blood, and the odor to substances produced in the lesion by the bacteria, especially by the vibrios.

The vibrio, although aerobic, motile, flagellated, curved and gram-negative, has been confused with the fusiform bacillus. Furthermore, although it is generally believed that the spirochete and the fusiform

5. Miller, W. D.: *The Micro-Organisms of the Human Mouth*, Philadelphia, S. S. White Dental Manufacturing Company, 1890, p. 80.

6. Vincent, M. H.: *Ann. Inst. Pasteur* **13**:609, 1899.

7. Plaut, H.: *Deutsche med. Wchnschr.* **49**:920, 1894.

8. Vincent, M. H.: *Ann. Inst. Pasteur* **10**:488, 1896; **13**:609, 1899.

TABLE 2.—Cases of Pulmonary Abscess and of Pulmonary Gangrene at Mount Sinai Hospital, July 1923 to July 1933

Num- ber of Cases	Sex		Age		Compli- cating Bron- chitis or Pneu- monia	Postoperative		No Anes- thesia	Location*					Arsenic Treatment		No Arsenic Treatment†		Postmortem Examination
	M	F	Infants and Chil- dren	Adults		General Anes- thesia	Local Anes- thesia		RU	RM	RL	LU	LL	Recov- ered	Died	Recov- ered	Died	
Staphylococcal bac- teremia or pyemia with embolic pul- monary abscesses	14	9	1	22	16
Pulmonary abscess (bronchogenic)	10	2	8	4	8	3 (1 oral opera- tion)	1 (nonoral opera- tion)	..	2	1	2	2	4	3	7	4: 1 assoei- ated with bacteremia caused by B. pyocyaneus
Miller-Vincent's pulmonary infection (pulmonary spirochetosis)	39	25	7	32	17	17 (8 oral opera- tions)	4 (2 oral opera- tions)	1 (oral opera- tion)	14	7	18	6	15	17	8	3†	11	10
Gangrene.....	6	4	0	6	4	1 (nonoral opera- tion)	..	1 (oral opera- tion)	1	0	4	1	3	6
Pneumonitis.....	8	7	0	8	5	2	4	4	4	6	1§	1	..	0
Bronchitis.....	2	2	0	2	1	1 (following gunshot wound)	2	1	1	0
Pleurisy.....	55	38	17	7	48				0
Total Miller-Vincent's infection.....	90																	
Grand total.....																		

* The abbreviations for location are: RU, the upper lobe of the right lung; RM, the middle lobe of the right lung; RL, the lower lobe of the right lung; LU, the upper lobe of the left lung, and LL, the lower lobe of the left lung.

† Some patients in this group received one treatment within four days of death.

‡ One was discharged the day after admission to the hospital.

§ There was active tuberculosis in the upper lobe of each lung.

bacillus live in symbiosis, there is no evidence in cultures that the presence of one favors the growth of the other, and, rather than one anaerobe favoring the growth of another in an aerobic environment, it is more likely that the vibrio, with its striking avidity for free oxygen (forming a surface pellicle in broth culture), is the symbiotic agent making possible the growth of the anaerobic oral spirochetes and anaerobic fusiform bacilli in the mouth and elsewhere.

The presence of spirochetes and fusiform bacilli in pulmonary gangrene was first reported in 1905 by Rona,⁹ who believed not only that these organisms produced the gangrene but that carious teeth were their source. Supporting these observations are those of Buday,¹⁰ reported in 1910. In a study of thirty-five cases of bronchial, broncho-pulmonary and pulmonary gangrene, Buday found innumerable spirochetes, fusiform bacilli and comma bacilli in the involved areas. In the bronchial lesions, the fusiform bacilli and comma bacilli were present in larger numbers than the spirochetes. In the gangrenous areas of the lungs, however, the spirochetes predominated, innumerable organisms of this type being present not only in the necrotic tissue but also at the margins toward the intact portion of the lung. From a careful microscopic study of his cases, Buday concluded that in acute bronchogenic gangrene of the lung, spirochetes, fusiform bacilli and comma bacilli are, in the majority of cases, the causative agents and not secondary invaders.

More important in establishing the etiologic relationship of these organisms to gangrene than their presence in early gangrenous areas and at the margin of more advanced ones is the fact that, with material containing them, similar lesions have been produced in animals (Veszpremi;¹¹ Loygue, Bonnet and Peyre;¹² Kline;¹³ Pilot and Davis;¹⁴ Smith¹⁵). Furthermore, Smith,¹⁶ with combined pure cultures of *T. microdentium*, an anaerobic hemolytic streptococcus, a small fusiform bacillus and a vibrio, succeeded in producing the lesion in rabbits after passage of the combined organisms through mice and guinea-pigs.

9. Rona, S.: *Arch. f. Dermat. u. Syph.* **74**:171, 1905.

10. Buday, K.: *Beitr. z. path. Anat. u. z. allg. Path.* **48**:70, 1910.

11. Veszpremi, D.: *Centralbl. f. Bakt. (Abt. 1)* **38**:136, 1905; **44**:408, 1907; **45**:15, 1908.

12. Loygue, M. G.; Bonnet, H., and Peyre, E.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **42**:1099, 1918.

13. Kline, B. S.: *Experimental Gangrene*, *J. Infect. Dis.* **32**:481, 1923.

14. Pilot, I., and Davis, D. T.: *Studies in Fusiform Bacilli and Spirochetes*, *Arch. Int. Med.* **34**:313 (Sept.) 1924.

15. Smith, D. T.: *Experimental Aspiratory Abscess*, *Arch. Surg.* **14**:231 (Jan.) 1927.

16. Smith, D. T.: *Fuso-Spirochetal Disease of the Lungs Produced with Cultures from Vincent's Angina*, *J. Infect. Dis.* **46**:303, 1930.

Although pulmonary gangrene almost invariably results from the aspiration of oral spirochetes, fusiform bacilli and vibrios from the mouth, it has been reported¹⁷ following embolism from putrid puerperal infections, gangrenous decubitus ulcers and degenerating tumors of the intestines and female genitals. The form and situation of early pulmonary lesions of this type are much like those following embolism of pyogenic organisms.

TABLE 4.—*Results of Tests for Syphilis in Cases of Infection with the Miller-Vincent Organism*

	Reaction	Wassermann Test	Diagnostic Slide Test
In cases with no evidence of syphilis.....	Negative	14	7
	Positive	0	0
	Doubtful	2	1
		1 anticomple- mentary	
In cases with evidence of syphilis.....	Positive	2	1
	Negative	2	2

SUMMARY

Table 2 summarizes the ninety cases of pulmonary abscess and of pulmonary gangrene and other types of Miller-Vincent's infection of the lung observed at Mount Sinai Hospital in the past ten years.

The fifty-five cases of Miller-Vincent's pulmonary infection in this series are described briefly in table 3.

Table 4 summarizes the results of tests for syphilis. It shows that in cases of infection with the Miller-Vincent organisms the blood did not give positive reactions in tests for syphilis unless this disease also was present.

17. Lauche, A.: Die Entzündungen der Lunge und des Brustfelles, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 3, pt. 1, p. 862.

TREATMENT OF CARDIOVASCULAR SYPHILIS

A STUDY OF THE DURATION OF LIFE IN EIGHTY TREATED AND UNTREATED PATIENTS WITH AORTIC ANEURYSM AND AORTIC REGURGITATION

ERNEST K. STRATTON, M.D.

SAN FRANCISCO

In 1930 Moore and Danglade^{1a} published an article on the treatment of cardiovascular syphilis. They together with Reisinger^{1b} followed this in 1932 with a similar article. These articles were particularly valuable because, with the use of various self-explanatory charts, they detailed the facts which many older clinicians had failed to record in the analysis of the effects of specific treatment on cardiovascular syphilis.

Inasmuch as there have been published only five other papers in which similar data have been recorded,² it seemed to the San Francisco Heart Committee and to me that a compilation of statistics made from the records of the various San Francisco hospitals according to the excellent chart forms originated by Moore and his co-workers would be an interesting contribution. The following statistics have been assembled with the courteous cooperation of the Medical Department of the Stanford University Hospitals, the University of California Hospital and the San Francisco County Hospital.

On this basis, the patients are divided into the following four treatment groups:

Group 1.—Those who received no treatment or very little (one or two injections of arsphenamine or three or four injections of bismuth or inunctions of mercury) for less than a month.

These statistics were assembled and the charts prepared with the help of Miss Rosemary T. Kobes, R.N., Cardiac Field Worker, San Francisco Heart Committee.

1. (a) Moore, J. E., and Danglade, J. H.: Treatment of Cardiovascular Syphilis: A Study of the Duration of Life in One Hundred and Forty-One Treated and Untreated Patients with Aortic Regurgitation and Aortic Aneurysm, *Am. Heart J.* **6**:148 (Oct.) 1930. (b) Moore, J. E.; Danglade, J. H., and Reisinger, J. C.: Treatment of Cardiovascular Syphilis: Results Obtained in Fifty-Three Patients with Aortic Aneurysm and in One Hundred and Twelve with Aortic Regurgitation, *Arch. Int. Med.* **49**:879 (June) 1932.

2. Reid, M. D.: Prognosis of Specific Aortitis, *J. A. M. A.* **73**:1832 (Dec. 13) 1919. Cotton, F. F.: Cardio-Aortic Syphilis and Its Treatment, *Brit. M. J.* **1**:855, 1926. Conybeare, J. J.: Treatment of Aortic Aneurysm by Anti-Syphilitic Remedies, *Guy's Hosp. Rep.* **74**:163, 1924. Herrmann, G., and Jamison, C.: Treatment of Cardiovascular Syphilis with Especial Reference to Aortic Regurgitation with Congestive Heart Failure, *Am. J. Syph. & Neurol.* **15**:1, 1932. Barnett, C. W.: Effect of Specific Treatment in the Prognosis of Syphilis of the Cardiovascular System, *Arch. Dermat. & Syph.* **28**:1 (July) 1933.

Group 2.—Those who were treated for a period of from six to twelve weeks (the equivalent of one course of arsenical treatment or one long course of treatment with a heavy metal).

Group 3.—Those treated for a period of from three to twelve months (roughly the equivalent of a long course of treatment with an arsenical plus a long course of treatment with a heavy metal).

Group 4.—Those treated for more than a year.

I have investigated 750 history charts bearing the diagnosis of cardiovascular syphilis. Of this number, 200 bore the definite diagnosis

TABLE 1.—*Patients with Aneurysm: Treatment, Group 1*

Patient	Age	Living or Dead	Duration of Life (Months) Until Death or Last Observation Measuring from		Cardiac Failure		Duration of Symptoms Before Treatment, Mos.	Aortic Regurgitation Also present
			Onset of Symptoms	Start of Treatment	Before Treatment*	After Treatment		
1	57	D	2	1	A 1	1
2	63	D	5	2	C 1, A 1	3	Yes
3	40	D	6	2	C 2	4	Yes
4	62	D	6	3	C 2	3
5	50	D	7	2	C 1, A 1	5	Yes
6	37	D	8	..	C 2	8	Yes
7	57	D	8	4½	C 1, A 1	3½	Yes
8	48	D	9	3	A 1	6
9	51	D	11	1	C 2, A 1	10
10	60	D	11	4	C 2	7
11	60	D	12	3	C 2, A 1	9
12	46	D	12	1	C 1, A 1	11
13	59	D	13	1	C 1	12
14	66	D	14	..	C 2, A 1	14
15	72	D	16	15	C 2	1
16	55	D	17	10	C 2, A 1	7	Yes
17	49	D	17	15	A 1	2	Yes
18	58	D	19	4	C 2	15	Yes
19	61	D	29	11	C 1, A 2	18
20	58	D	34	21	C 1, A 1	13
21	75	D	36½	½	C 1, A 1	36
22	49	D	38	19	C 1	19
23	52	D	39	8	C 2, A 1	31	Yes
24	47	D	60	5	C 3, A 2	55	Yes
25	57	D	64	4	C 2, A 1	60
26	50	D	109	1	C 1	108
27	41	D	5	13	C 2, A 1	0
28	45	L	106	10	C 1	96	Yes

* In this and subsequent tables A means anginal failure and C congestive failure; 1, 2 and 3 are used to represent the degrees of severity of symptoms.

of either aneurysm or aortic regurgitation, and of these patients with aneurysm or aortic regurgitation 92 were known to be either dead or in active attendance at the clinics of the three institutions at the time these statistics were compiled.

Forty-three of the patients had aneurysm; 4 of these were living and 39 were dead. Forty-nine patients had aortic regurgitation, 14 of these were living and 35 were dead. Twelve patients from these two groups (11 in group 1 and 1 in group 2) had both these conditions. I had, therefore, a total of 80 patients from whose histories I finally compiled the accompanying tables.

Since none of these patients had at any time been under my observation, the data herein presented are those transcribed from their history charts. There was nothing in their histories to indicate that any of them had received antisyphilitic treatment for their cardiovascular lesions before admission to the clinics.

TABLE 2.—*Patients with Aneurysm: Treatment, Groups 2, 3 and 4*

Patient	Age	Living or Dead	Duration of Life (Months) Until Death or Last Observation Measuring from		Cardiac Failure		Duration of Symp- toms Before Treat- ment, Mos.	Aortic Regur- gitation Also Present
			Onset of Symptoms	Start of Treatment	Before Treat- ment	After Treat- ment		
Group 2								
1	45	D	8	7	C 2	1	N..
2	61	D	19	18	C 2	1
3	50	L	27	17	A 1	10
4	40	D	41	29	C 1	12
5	51	D	51	29	C 2, A 1	22
6	65	D	79	43	C 2, A 2	36	Yes
Group 3								
1	47	L	55	54	C 1, A 1	1
2	57	D	21	18	C 2	3
3	47	L	15	7	Pressure	8
4	55	D	52	28	C 2, A 2	24
5	48	L	65	10	Pressure	55
Group 4								
1	37	D	24	144	C 2	None
2	50	D	54	372	C 2	None
3	52	D	44	42	C 1	2
4	46	D	41	36	C 2, A 1	5

TABLE 3.—*Effect of Treatment on Prolongation of Life in Patients with Aneurysm of the Aorta (Forty-Three Cases; Four Living, Thirty-Nine Dead)*

Treatment Group	Average Age, Yrs.	Patients in Group	Patients Living	Patients Dead	Average Duration of Symptoms Before Treatment, Mos.	Average Duration of Life (Months) Until Death or Last Observation Dating from	
						Onset of Symptoms	Start of Treatment
Group 1	54.4	28	1	27	19.9	25.4	5.8
Group 2	52	6	1	5	13.7	37.5	23.8
Group 3	50.8	5	2	3	18.2	41.6	23.5
Group 4	46.2	4	0	4	1.8	40.7	148.5

It is interesting to note that practically every one of these patients complained of some type and degree of cardiac failure before anti-syphilitic treatment was instituted. In the columns headed "Cardiac Failure" I used the letter C and A to designate congestive and anginal failure, respectively, and the grades 1, 2 and 3 to denote the severity of the symptoms.

TABLE 4.—*Patients with Aortic Regurgitation: Treatment, Group 1*

Patient	Age	Living or Dead	Duration of Life (Months) Until Death or Last Observation Measuring from		Cardiac Failure		Duration of Symptoms Before Treat- ment, Mos.	Aneurysm Also Present
			Onset of Symptoms	Start of Treatment	Before Treat- ment	After Treat- ment		
1	36	D	3	2	C 3	1
2	56	D	3	2	C 1	1
3	38	D	3	1	C 2, A 1	2
4	62	D	3	1	C 2, A 1	2
5	50	D	4	1	C 2	3
6	63	D	5	2	C 2, A 1	3	Yes
7	58	D	6	2	C 2	4
8	60	D	6	None	C 2	6
9	40	D	6	2	C 2	4	Yes
10	50	D	7	2	C 1, A 1	5	Yes
11	57	D	8	4	C 2, A 1	4	Yes
12	37	D	8	None	C 2	8	Yes
13	40	D	14	2	C 2	12
14	49	D	15	None	C 2	15
15	49	D	16	14	A 1	2	Yes
16	55	D	17	10	C 2, A 1	7	Yes
17	51	L	18	13	C 1	5
18	58	D	19	4	C 2	15	Yes
19	48	L	21	192	C 3	None
20	56	D	25	1	C 1	24
21	43	D	24	None	C 2	24
22	68	D	26	24	C 2	2
23	52	D	39	8	C 2, A 1	31	Yes
24	47	D	60	5	C 3, A 2	55	Yes
25	39	D	68	8	C 2	60
26	45	L	106	10	C 1	96	Yes
27	56	L	119	111	C 1, A 1	8

TABLE 5.—*Patients with Aortic Regurgitation: Treatment, Groups 2, 3 and 4*

Patient	Age	Living or Dead	Duration of Life (Months) Until Death or Last Observation Measuring from		Cardiac Failure		Duration of Symptoms Before Treat- ment, Mos.	Aneurysm Also Present
			Onset of Symptoms	Start of Treatment	Before Treat- ment	After Treat- ment		
Group 2								
1	32	D	4	3	C 2, A 2	1
2	47	D	8	6	C 2	2
3	58	D	7	4	C 2	3
4	59	D	8	4	C 1	4
5	32	D	27	3	C 1	24
6	65	D	79	43	C 2, A 2	36	Yes
Group 3								
1	50	D	8	20	C 2, A 1	None
2	65	D	44	43	C 2	1
3	47	D	27	22	C 2, A 1	5
4	61	D	17	8	C 1, A 1	9
Group 4								
1	62	L	33	141	C 1	None
2	53	L	39	336	C 1	None
3	55	L	48	101	C 1	None
4	48	L	48	131	C 1	None
5	38	L	54	180	A 1	None
6	64	D	50	49	C 2, A 1	1
7	50	L	74	73	C 1	1
8	57	L	124	120	C 2	4
9	37	D	47	32	C 2, A 1	15
10	36	L	76	31	C 1	45
11	55	L	82	22	C 1	60
12	59	L	156	62	C 1	94

TABLE 6.—*Effect of Treatment on Prolongation of Life in Patients with Aortic Regurgitation (Forty-Nine Cases; Fourteen Living, Thirty-Five Dead)*

Treatment Group	Average Age, Yrs.	Patients in Group	Patients Living	Patients Dead	Average Duration of Symptoms Before Treatment, Mos.	Average Duration of Life (Months) Until Death or Last Observation Dating from	
						Onset of Symptoms	Start of Treatment
Group 1	50.5	27	4	23	14.8	24	15.6
Group 2	48.8	6	0	6	11.7	22	10.5
Group 3	55.8	4	0	4	3.8	24	23.2
Group 4	51.1	12	10	2	18.3	69.6	106.5

TABLE 7.—*Effect of Treatment on Prolongation of Life in Whole Group of Patients with Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation; Eighty Cases; Seventeen Living, Sixty-Three Dead)*

Treatment Group	Average Age, Yrs.	Patients in Group	Patients Living	Patients Dead	Average Duration of Symptoms Before Treatment, Mos.	Average Duration of Life (Months) Until Death or Last Observation Dating from	
						Onset of Symptoms	Start of Treatment
Group 1	53	44	4	40	16.5	24.3	11.9
Group 2	49	11	1	10	10.5	25.3	14.8
Group 3	53	9	2	7	11.8	33.7	23.3
Group 4	49.9	16	10	6	14.2	62.4	117.0

TABLE 8.—*Symptomatic Relief Resulting from Antisyphilitic Treatment in Cardiovascular Syphilis*

Treatment Group	Patients with Aneurysm			Patients with Aortic Regurgitation		
	Total Number	No. Who Obtained Symptomatic Relief	No. Who Obtained No Relief	Total Number	No. Who Obtained Symptomatic Relief	No. Who Obtained No Relief
Group 1	28	1	27	27	3	24
Group 2	6	0	6	6	1	5
Group 3	5	3	2	4	3	1
Group 4	4	2	2	12	6	6

TABLE 9.—*Influence of Treatment on Ability to Work in Cardiovascular Syphilis (Aneurysm and Aortic Regurgitation)*

Treatment Group	Patients with Data Available	A Number Unable to Work Before or After Treatment	B Number Unable to Work Before, but Able After Treatment	C Number Able to Work Before but Unable After Treatment	D Number Able to Work Before and After Treatment
Group 1	40	32	2	2	4
Group 2	10	7	1	..	2
Group 3	9	3	3	..	3
Group 4	13	1	2	1	9

Twenty-eight patients with aneurysm listed in table 1 had little or no antisyphilitic treatment, and therefore the information given in the column headed "Duration of Life Until Death or Last Observation, Measuring from Onset of Symptoms" represents the average life expectancy for such patients. The duration of symptoms before treatment would have practically no bearing on the outcome for this group. It may be significant that of this group, 11 patients or 39 per cent lived less than twelve months (an average of seven months) after the onset of symptoms, and 17 (61 per cent) lived from twelve to one hundred and nine months (an average of thirty-seven months).

It is to be regretted that table 2, which represents groups 2, 3 and 4 treated for aneurysms, does not list as many patients for each group as were listed for group 1. On the basis of the few cases recorded, however, it seems that antisyphilitic treatment in the case of syphilitic aneurysm is responsible for prolonging life for from twelve to sixteen months on the average (table 3).

In presenting the cases of aortic regurgitation table 4 represents 27 cases falling into group 1, and leads one to the same conclusion as table 1, representing the 28 cases of aneurysm falling into treatment group 1. Twelve of these patients or 44 per cent lived less than twelve months (an average of five months) after the onset of symptoms, and 15 (56 per cent) lived from twelve to one hundred and nineteen months (an average of thirty-nine months).

Again it seems that the lives of the few patients falling especially into group 4 were definitely prolonged by the use of antisyphilitic treatment (table 6).

COMMENT

Moore¹ has so completely covered the field of comment and deduction on similar charts that I have made no attempt to do other than offer these additional statistics in the hope that their inclusion may be of some value in ultimately arriving at a large enough total of similarly studied groups to make the findings conclusive.

RELATION OF ASTHMA TO SINUSITIS

WITH SPECIAL REFERENCE TO THE RESULTS FROM SURGICAL
TREATMENT

ROBERT A. COOKE, M.D.

AND

R. CLARK GROVE, M.D.

NEW YORK

From the many aspects that present themselves we have chosen to discuss in this paper the importance of disease of the sinuses in asthma and the evidence that infective asthma is an allergic reaction to bacteria or their products and that disease of the sinuses is usually the primary focus of infection; further, we present our data showing the effect of surgical intervention on the sinuses in asthma.

Wherever pathologic condition of the nasal passages is mentioned in connection with our cases of asthma, we refer to disease of the sinuses; as far as the literature is concerned, however, vasomotor changes, septal deviations and simple turbinal hypertrophies are included, and there is little or no attempt to differentiate the histologic type of disease of the sinuses, that is, the suppurative or the hyperplastic. In all our cases of asthma the membrane of the sinuses has been of the true hyperplastic type.

In a former paper ¹ we concluded that the hyperplastic membrane is primarily infective and represents a special reaction to bacteria determined by the allergic constitution of the person so infected; in other words, the thickening of the membranes is not a reaction to inhaled substances or to foods. This position is not universally conceded but was fully discussed in our former paper.

The recognition of the importance of disease of the sinuses in thoracic conditions is, oddly enough, of recent date. Bronchiectasis was described by Laennec ² in 1819, and pathologic conditions of the nasal

Read in part before the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., April 28, 1934.

From the Department of Allergy of the Roosevelt Hospital and the Department of Medicine of the New York Hospital and Cornell University Medical College.

1. Grove, R. C., and Cooke, R. A.: Etiology and Nature of Chronic Hyperplastic Sinusitis, *Arch. Otolaryng.* **18**:622 (Nov.) 1933.

2. Laennec, R. T. H.: *Traité de l'auscultation médicale et des maladies des poumons et du coeur*, Paris, Brosson and J. S. Chaude, 1819.

passages have been recognized almost as long, but it was not until 1916 that the importance of the association of the two lesions was noted by Sergeant.³ Two years before, however, Thompson⁴ had shown that the amount of secretion in bronchorrhea was influenced by treatment of the sinuses. Since that time there has grown up an enormous number of reports in the literature regarding this association of chronic disease of the sinuses with chronic nontuberculous infections of the chest.

Although this association of nasal and thoracic infection is established, the causal relationship is not, and some authors regard these conditions as concomitant manifestations of the same infection. The weight of opinion, however, is that disease of the sinuses is primary to chronic nontuberculous infections of the chest. This conclusion is based largely on the fact that relief from certain thoracic symptoms follows proper nasal therapy and on the explanation afforded by Mullin's⁵ work in 1919 on lymphatic drainage of the nasal sinuses. He showed that although there is no direct lymphatic connection between the nasal sinus and the glands of the hilus or the lungs, foreign material and bacteria were carried from the sinuses by the lymphatic glands to the duct, to the superior vena cava, to the right side of the heart and thence to the lungs. The bronchial and mediastinal glands were involved in all cases, and supposedly they are secondarily involved by lymphatic absorption from the lungs.

According to Adam,⁶ it was Herck who, in 1844, first recognized the importance of a nasal factor in asthma. Voltolini⁷ in 1872 recorded 11 cases of asthma in which relief followed nasal polyectomy.

Among the more recent reports is that of Adam,⁶ who found nasal lesions in 68 per cent of 850 cases, but from the context it is not clear whether he included septal deviations and vasomotor rhinitis.

Rackemann and Tobey⁸ are variously quoted as having found involvement of the sinuses in from 44 to 65 per cent of 1,074 cases of asthma. Grant⁹ gave his figures as 63 per cent in 107 cases.

3. Sergeant, Emile: *Histoire suggestive de quelques faux tuberculeux. Diagnostic différentiel de la tuberculose pulmonaire et des affections des voies respiratoires supérieures*, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1424, 1916.

4. Thompson, St. Clair: *Some of the Symptoms and Complications of Sinusitis*, Practitioner **92**:745, 1914.

5. Mullin, W. V.: *The Lymph Drainage of the Accessory Nasal Sinuses*, Tr. Am. Laryng., Rhin. & Otol. Soc., 1919, p. 23.

6. Adam, James: *Asthma*, ed. 2, St. Louis, C. V. Mosby Company, 1926, p. 97.

7. Voltolini, R.: *Die Anwendung der Galvanokaustic*, ed. 2, Vienna, Wilhelm Braumüller, 1871, pp. 246 and 312.

8. Rackemann, F. M., and Tobey, H. G.: *Studies in Asthma: IV. The Nose and Throat in Asthma*, Arch. Otolaryng. **9**:612 (June) 1929.

9. Grant, J. D.: *Nasal Disease in Relation to Asthma*, Practitioner **90**:914, 1913.

Gottlieb¹⁰ found asthma associated with sinusitis in only 26 per cent of 117 cases. Kern and Schenck¹¹ found that of 400 cases of asthma there were 70 per cent with clinical evidence and 87.5 per cent with roentgen evidence of disease of the sinuses. Chobot,¹² in studying children up to 15 years of age, found roentgen evidence of sinusitis in 41 per cent of the patients observed in 1930 and in 67 per cent of those observed in 1933.

In a recent study¹³ which one of us (R. A. C.) published in 1932 688 cases were studied consecutively, and a complete diagnosis was reached. Nasal examination was made in all, and roentgen examination of the sinuses in 90 per cent, of the cases, and it was found that disease of the sinuses was present in 38 per cent of 257 patients in whom asthma developed between the ages of 10 and 30, in 65 per cent of 171 in whom it appeared between the ages of 30 and 50 and in 83 per cent of 42 in whom it became manifest after they reached 50 years of age. Such figures clearly set forth the importance of disease of the sinuses in asthmatic patients, but when one speaks of asthma of infective origin one does not necessarily imply that the disorder has its origin in disease of the sinuses.

An attack of asthma may be caused by primary acute bronchitis or bronchopneumonia, or it may be secondary to acute—rarely to chronic—tonsillar or pharyngeal lesions with pulmonary and bronchial extension. This is certainly true of infants and young children, whose sinuses are still rudimentary, but the same course of events also occurs in older children and adults. Of the 688 cases which formed the basis of the study referred to, infection was the sole cause of asthma in 34 per cent, and infection combined with sensitization, such as sensitization to pollens, danders or foods, was a cause in an additional 15 per cent; thus a total of 49 per cent of all the cases of asthma were caused by infection.

If one excludes cases of asthma occurring during the first decade of life, since the infections occurring at that age practically always are acute or are secondary to foci in the lymphoid tissue of the pharynx and not in the sinuses, there remain 470 cases; in 248, or 53 per cent, of these infection was a cause, and with the exception of perhaps about

10. Gottlieb, M. J.: Relation of Intranasal Disease in Production of Bronchial Asthma, *J. A. M. A.* **85**:105 (July 11) 1925.

11. Kern, R. A., and Schenck, H. P.: Chronic Paranasal Sinus Infection: Relation to Diseases of the Lower Respiratory Tract, *Arch. Otolaryng.* **18**:425 (Oct.) 1933.

12. Chobot, Robert: The Incidence of Sinusitis in Asthmatic Children, *Am. J. Dis. Child.* **39**:257 (Feb.) 1930; Asthma in Children, *ibid.* **45**:25 (Jan.) 1933.

13. Cooke, Robert A.: Infective Asthma: Indications of Its Allergic Nature, *Am. J. M. Sc.* **183**:309, 1932.

8 per cent in which primary pulmonary infection was present, in the rest, or practically 45 per cent (92 per cent of the cases of infective asthma), disease of the sinuses was the important primary focus of the infection causing asthma. The 8 per cent in which disease of the sinuses did not occur included cases of primary acute bronchial and pulmonary infections and of chronic infections with ordinary pathogens as well as with spirochetes and molds.

If one stops to inquire why in certain patients the symptom of asthma is superimposed on nasal and thoracic infections, the only answer that can be made is that these persons have an allergic constitution and become sensitized to bacteria or their products.

The proof of this is found first in the family history. In the study of the 688 cases previously alluded to, a history of allergy in previous generations was found in 45 per cent of 235 cases of purely infective asthma as contrasted with 52 per cent of the 349 cases of asthma due purely to allergy of the "skin-sensitive" type. Further, other allergies existed in 30 per cent of the cases of infective asthma. Again, eosinophilia was present in over 50 per cent of the patients with infective asthma, and eosinophil cells were present in the sputum of practically 100 per cent of the patients whose sputum was examined during an attack. The bronchial mucous membrane is known to be infiltrated with such cells. Eosinophilia was also observed in the discharge from the sinuses and in the hyperplastic sinus membrane of practically all the patients examined.

As a matter of fact, in all the cases of our series in which operation was performed the membrane of the sinuses was of this hyperplastic type. None of the patients with asthma exhibited the true pyogenic membrane associated with suppurative sinusitis, although an acute exacerbation accompanied by discharge of some purulent mucoid exudate was observed from time to time.

Eosinophilia has come to be regarded as a part of the cellular response to the allergic reaction. A more complete survey of this point with the data has been given in the paper¹³ on infective asthma.

Another proof of the allergic nature of the infection lies in the capacity of the patients to respond with symptomatic asthma to an injection of vaccine, particularly to injection of an autogenous vaccine.

Of the mechanism of the allergic reactions to bacteria and their products, little is known. Immunologically the manifestation is not at all similar to the reactions to pollen in which an urticarial wheal is formed in the skin immediately as a result of a cutaneous test and an immediate reaction in the membranes results from contact with the pollen such as that which occurs in cases of hay fever and asthma due to an overdose of pollen extract. Also passive transfer of the sensitization is accomplished with the serum of these sensitive patients.

On the contrary, in infective asthma the cutaneous reaction with the bacterial extract or suspension is delayed for from twenty-four to forty-eight hours, if it occurs at all. An overdose of vaccine, if it produces asthma, does so after twelve, twenty-four or even forty-eight hours (symptomatic reaction). There is no passive transfer of the sensitization. What, then, are the facts regarding the cutaneous test with vaccines in cases of asthma? Among 120 patients with infective asthma who have been operated on by one of us (R. C. G.) at the clinic, there were 70 on whom tests with autogenous vaccine were made, and observations were carried out with such care that the results are worth recording. Thirty-eight of these 70 probably had symptomatic asthma due to injection of vaccine, but in 27 an attack of asthma was definitely produced by the injection of vaccine. Nineteen of the 27 gave a delayed positive reaction (from twenty-four to forty-eight hours) to an intradermal test with the vaccine that caused asthma. In none was the immediate reaction positive. Eight of the 27 patients gave negative reactions to the intradermal vaccine which produced asthma.

If one looks at the other side of the picture, there were 32 patients in whom no symptoms of asthma resulted from injections of vaccine, but 25, or 75 per cent, of these gave delayed positive cutaneous reactions to the vaccines. We cannot therefore agree with Thomas and Touart¹⁴ and others who contend that in cases of asthma a diagnostic significance is to be attached to cutaneous reactions to vaccine. It is our opinion that the only reliable test is the reproduction of the asthma and that this symptomatic test presents difficulties and dangers. We believe, therefore, that the cutaneous test is of no value in determining the organism responsible for asthma.

The evidence that disease of the sinuses is the primary focus is to be found in clinical observation on patients with infective asthma and in the results obtained in patients with asthma as a consequence of surgical treatment of the nasal sinuses. In all cases in which it has been possible to observe the development of bacterial asthma in adults, there has been a stage of hyperplastic sinusitis without asthma lasting for from five to ten years or longer. Opportunity to watch this development has been afforded in the large group of patients with hay fever who at first had acute or supposedly acute attacks of sinusitis with the development of hyperplastic changes and often with nasal polypi and who eventually had attacks of bronchitis with each exacerbation of the sinusitis and finally showed signs and symptoms of asthma.

Satisfactory evidence of the primary importance of disease of the sinuses is seen in the effects of surgical treatment of the sinuses on

14. Thomas, W. S., and Touart, M. D.: Late Vaccine Skin Reactions, *J. Allergy* 4:242, 1933.

asthma even of many years' duration. The results recorded in the literature at present are not exceeding encouraging. Heatly and Crowe¹⁵ reported improvement in 53 of 62 cases but "only one case was enthusiastic enough to describe himself as 'cured' after three years." However, it is not made clear whether operations on the septum, turbinate bones, tonsils and adenoids were performed alone or in connection with operations on the sinuses.

Rackemann and Tobey⁸ reported 91 cases of asthma in which the infection of the sinuses was treated surgically. In 14 per cent cure resulted after a period of more than two years; in 46 per cent improvement occurred; in 31 per cent there was no improvement, and in 9 per cent death occurred. Weille¹⁶ in 1930 stated that of 40 patients treated surgically but 50 per cent have a chance for relatively long continued favorable changes in their asthma. Schenck and Kern,¹⁷ Vaughan¹⁸ and Warner and McGregor¹⁹ reported less favorable results.

But it is difficult from the reports in the literature to evaluate the results of surgical treatment in disease of the sinuses as many cases have not been studied for sensitization, which commonly coexists, and it is not made clear whether the pathologic condition of the sinuses is completely eradicated.

We recently made a study of 120 cases of asthma which included a complete survey of the sensitization and rhinologic conditions. Operations had been performed in all cases, and the postoperative period of observation extended from six months to three and a half years. Patients not reporting within a month have been excluded. Fifty-five cases of infective asthma and 65 of infective asthma associated with allergy of the "skin-sensitive" type constituted the series. These cases have been further divided according to the time since operation into three groups, observed for from six months to one year, from one to two years and from two to three and a half years, respectively. These groups have been further divided into two subgroups: subgroup 1, in which all indicated surgical treatment had been completed, and subgroup 2, in which indicated surgical treatment for one reason or another was still incomplete. The

15. Heatly, C. A., and Crowe, S. J.: Asthma and Infections of the Accessory Nasal Sinuses: A Study Based on Sixty-Two Cases, *Bull. Johns Hopkins Hosp.* **34**:410, 1923.

16. Weille, F. L.: Studies in Asthma: XVIII. The Surgical Treatment of Chronic Sinusitis in Asthma, *J. A. M. A.* **100**:241 (Jan. 28) 1933.

17. Schenck, H. P., and Kern, R. A.: An Evaluation of the Therapeutic Effect of the Caldwell-Luc Operation in Bronchial Asthma, *J. Allergy* **3**:296, 1932.

18. Vaughan, W. T.: Some Rhinologic Aspects of Allergy, *J. Allergy* **4**:127, 1933.

19. Warner, W. P., and McGregor, G.: Effect of Radical Antrum Surgery on Bronchial Asthma, *J. Laryng. & Otol.* **48**:595, 1933.

patients with infective asthma only have been treated surgically, and a few have received vaccine therapy in addition. In those with infective asthma associated with allergy as shown by positive cutaneous tests the allergic condition has been taken into account and treated by injection or by elimination.

As shown in table 1, the operations performed were: ethmoidectomy, sphenoidectomy, enlargement of the frontal duct and radical operation on the antrum (Caldwell-Luc type). Rarely was a polypus alone removed, but usually the operation on the sinuses was performed at the same time, because we believe that the source of infection is in the attachment or underlying membrane. Submucous resection and trimming of the inferior turbinates were performed on these patients only in connection with the work on the sinuses or because of marked obstruc-

TABLE 1.—Pathologic Conditions of the Nasal Passages and Operations on the Sinuses in 120 Cases of Infective Asthma

Pathologic Conditions	Single	Bilateral	
Chronic sinusitis, ethmoid.....	21	82	
Chronic sinusitis, maxillary.....	17	84	
Chronic sinusitis, sphenoid.....	15	56	
Chronic sinusitis, frontal.....	30	13	
Chronic sinusitis, with nasal polyps.....	25	71	
Pansinusitis	40
Cysts of the antrum.....	10
Operations			
Ethmoidectomy	35	58	
Sphenoidectomy	15	28	
Radical operation on the antrum (Caldwell-Luc).....	30	27	
Enlargement of frontal duct.....	6	..	9
Submucous resection	17	
Previous window resection of the antrum.....	31	..	63
Previous operations on the sinuses, ethmoid and sphenoid.....	
Total number of operations on the sinuses.....	257		

tion, and not as isolated operations for asthma. The greater portion of the middle turbinate was always removed when the ethmoid sinus was exenterated; a smaller portion was removed if the operation was limited to the sphenoid sinus. The usual Caldwell-Luc type of radical operation on the antrum was performed, and we shall not go into any detail about the surgical procedures. The type of operation on the antrum or on the ethmoid or sphenoid sinus is not the important element, but rather the thoroughness with which the procedure is carried out. Nor are we concerned in this paper with the immediate effect of the operation on these asthmatic patients; but we wish to emphasize the fact that even though the operations on the antrum were performed under general anesthesia there was no pulmonary complication in this series, and, with the exception of one case, there was no operative shock. Too many general practitioners, as well as some rhinologists, are appalled by the word "radical" attached to this opera-

tion and therefore will not recommend its performance. However, this need not be, and we suggest that the procedure be called simply the "complete" operation on the antrum.

There were no cases in which there was sufficient pathologic evidence to justify an external operation on the frontal sinus, although in several cases enlargement of the intranasal frontal duct was performed with good results. The intranasal operation, ethmoidectomy or sphenoidectomy, if needed, was first performed with the patient under local anesthesia, and on the following day, or as soon as the general condition of the patient permitted, the complete Caldwell-Luc operation on the antrum was performed. Our results show that when the intranasal operation and the operation on the antrum are both needed one procedure alone seldom suffices, and we believe that operations on the antrum, for example, frequently produce unsatisfactory results because a diseased ethmoid or sphenoid sinus is not treated properly at the same time.

The intranasal operation can often be performed bilaterally at one sitting. Also both antrums may be radically operated on in a single procedure.

Infection of the ethmoid sinuses was associated with infection of the sphenoid sinus in 65 cases and with infection of the antrum in 95 cases. The sphenoid sinus was seldom involved without coexistent involvement of the ethmoid sinuses or of the antrum. The frontal sinus was least frequently involved. One antrum alone was involved in 17 cases; the involvement was bilateral in 84 cases. In 80 per cent of our 120 cases nasal polypi were present. The high percentage may have been due to the fact that a large majority of the patients had undergone nasal operations previously and that patients with polypi come to operation more frequently than others.

The ethmoid and sphenoid sinuses were operated on jointly in 38 cases, 28 of the operations being bilateral. Thirty patients had a single Caldwell-Luc operation, and 27, a bilateral operation; 21 had unilateral operations on the ethmoid sinus and antrum, and 20 bilateral operations on these cavities. Operation on the ethmosphenomaxillary group was performed unilaterally in 10 cases and bilaterally in 12.

The interesting points brought out in this follow-up study of the postoperative course of our patients (table 2) are as follows:

1. Eighty-four, or 70 per cent, of the entire series showed definite improvement.

2. Of those who had received complete surgical treatment (subgroup 1), 86 per cent showed improvement, as contrasted with 39 per cent, the figure for those on whom the surgical treatment was incomplete (subgroup 2).

3. Considering only the groups who received complete surgical treatment, cure or nearly complete cure (table 2) occurred in 29 per cent of the patients in the group from six months to one year, in 36 per cent of those followed for from one to two years (group 2) and in 51 per cent of those followed for from two to three and a half years (group 3).

TABLE 2.—Analysis and Results in 120 Cases of Infective Asthma with Disease of the Sinuses Surgically Treated*

TABLE 2.—Analysis and Results in 120 Cases of		the Sinuses Surgically Treated*		
		Results		
		+	++	+++
Postoperative Follow-up Period				
Asthma (120 cases)		2	4	2
Infective asthma (55 cases)		3	6	3
Complete surgical treatment (34 cases)		1	3	10
Incomplete surgical treatment (21 cases)		3	1	0
Asthma combined with allergy (65 cases)		3	1	0
Complete surgical treatment (45 cases)		7	4	2
Incomplete surgical treatment (20 cases)		2	4	3
Infective asthma (total number of cases)		1	6	6
Asthma combined with allergy (total number of cases)		2	12	9
Results (total number of cases)		5	0	0
Improvement in total number of cases (120)		1	0	1
		6	5	2
		36	46	38
		Complete Operation		Incomplete Operation
		++ and +++		++ and +++
		+	+	+
		6	28	13
		5	40	12
		11	68	25
		or 86% improvement		or 39% improvement
				36
				84
				or 70%

* The symbol + indicates slight or no improvement in asthma; ++, definite improvement; +++, no asthma or a rare attack.

On the other hand, results designated as slight improvement and definite improvement (table 2), which really represent the total improvement, occurred in 77 per cent, 85 per cent and 91 per cent, respectively, in the three groups. The fact that the percentages increased with the passage of time from operation is perhaps the most hopeful point to be gleaned from these studies. We do not anticipate any striking results in the first six months, and we have not even considered such

results in our study. The frequent lack of immediate improvement and the gradual improvement with the passage of time indicate to us the deep-seated nature of the infection with which allergy exists, the seat of that infection probably being located in the bronchial glands and the mucosa. After removal of the primary focus these secondary foci heal slowly. The patients who do well from the beginning and remain well for three and a half years may never have had such bronchial involvement. In those who never do well after complete surgical treatment the capacity of the secondarily involved glands to heal appears to be lacking. It ought to be possible to determine whether or not such assumptions are correct, and some of our present studies are being directed to that end.

The fact that in 12 cases in which window resection of the antrum had been performed the complete operation on the antrum later became necessary because of continued asthma and that in 9 of these definite improvement then occurred is a strong point in favor of the complete operation when indicated. Also we noticed that after window resection the passages became blocked frequently by the continued growth of polypi in the antrum and that infections of the upper portion of the respiratory tract necessitating treatment of the sinuses were more frequent before than after the complete operation. Furthermore, when the indicated surgical treatment had been completed, the patients who later had an acute infection of the upper portion of the respiratory tract frequently did not have a recurrence of attacks of asthma. We¹ have previously presented evidence that the infection is in the deeper layers of the membrane of the sinuses and that to eliminate this an operation more extensive than simple window resection is needed. The improvement in general health, that is, in weight, appetite, strength, morale and such associated conditions as arthritis, was quite striking in at least 50 cases. The condition of the sinuses, which is important to the patient regardless of asthma, was entirely satisfactory in 100 cases at the last examination, while in 20 cases there was a recurrence of polypi. In 14 of the latter cases surgical treatment had been incomplete.

In evaluating the effect of surgical treatment of the sinuses on asthma it is essential to analyze the case thoroughly not only for the completeness of the elimination of nasal infection by operation but also as to the extent of the treatment of any associated allergy of the "skin-sensitive" type and any continuing extranasal infection. Infection with molds (fungi) and spirochetes, and tuberculosis and infections of the teeth and tonsils are important complicating factors in cases of infective asthma. This is well illustrated by the fact that 6 of our patients who showed no improvement had a complicating bronchial moniliasis that did not respond to any treatment.

COOKE-GROVE—ASTHMA AND SINUSITIS

Two of our patients also seemed to do well after ovarian and uterine operations, although we were unable to evaluate the result properly because of the previous operations on the sinuses. Certainly we have found that in some cases, as far as prolonged freedom from asthma is concerned, dust and other allergens may be important factors and cannot be neglected simply because the patient has had some pathologic condition of the sinuses and has been operated on.

SUMMARY

In asthma, disease of the sinuses is an important primary focus of infection. Of 248 cases of infective asthma beginning after the patient was 10 years of age, sinusitis was an etiologic factor in 92 per cent.

We believe that infective asthma is the result of an allergic reaction to bacteria or their products. This is evidenced by the frequency of allergy in the preceding generations, by the associated allergies, by the eosinophilic response of the membranes of the sinuses, by the condition of the exudate, sputum and blood and, lastly, by the reproduction of symptomatic asthma through injections of vaccine.

Cutaneous reactions to vaccine cannot be relied on to determine the organism causing asthma.

One hundred and twenty patients with asthma associated with disease of the sinuses which was treated surgically were observed post-operatively for from six months to three and a half years. In 70 per cent of the patients improvement occurred. We believe that results should be evaluated according to the completeness or incompleteness of the surgical procedure since 86 per cent of the patients who received complete surgical treatment (subgroup 1) showed improvement as contrasted with 39 per cent, the figure for those on whom surgical treatment was incomplete (subgroup 2). Striking results should not be expected too soon after operation. Increasing percentages of improvement were noted in our series with the passage of time, probably owing to the gradual elimination of infection in the deep-seated bronchial glands or mucosa.

In analyzing the effect of surgical treatment of the sinuses in asthma, extranasal infections, such as those due to molds (fungi) or spirochetes, as well as any associated allergy of the "skin-sensitive" type, must be considered.

PYOTHORAX DUE TO FUSOSPIROCHETAL INFECTION

RUSSELL A. FLACK, M.D.

LAFAYETTE, IND.

Fusiform bacilli and Vincent's spirilla are frequently credited with causing severe infections in the mouth and pharynx. During the last few years a number of cases have been reported in which fusospirochetal infection was considered responsible for severe pulmonary infection.

Since the first descriptions of the fusospirochetal organisms by Plaut¹ in 1894 and Vincent² in 1899, the organisms have been known to exist in the upper respiratory tract in the absence of any evidence of acute infection. Controversy still exists as regards the pathogenicity of these organisms. Smith³ has experimented at length and has reported that so-called fusospirochetal pulmonary infections are probably due to a symbiosis of a spirochete, a fusiform bacillus, a vibrio and a coccus. Lichtenberg, Werner and Leuck,⁴ who recently reviewed the literature in regard to authentic proof of the pathogenicity of these organisms and reported experimental data of their own, concluded that the pathogenicity of the fusospirochetal organisms is still open to question. Nevertheless cases are numerous in which clinical signs follow fairly characteristic patterns and in which bacteriologic examinations demonstrate that the fusospirochetal organisms are greatly in preponderance. With full realization that fusospirochetal infection may or may not be a true bacteriologic entity, I wish to report three cases in which pyothorax accompanied severe pulmonary infection and in which fusospirochetal organisms appeared to constitute the important etiologic factor.

The clinical course in the cases reported indicates that pyothorax associated with large numbers of fusospirochetal organisms causes certain clinical signs not encountered in the more common types of

From the Department of Medicine, the Arnett-Crockett Clinic.

1. Plaut, H. C.: Studien zur bakteriellen Diagnose der Diphtherie und der Anginen, Deutsche med. Wchnschr. **20**: 920, 1894.

2. Vincent, M. H.: Recherches bactériologiques sur l'angine à bacillus fusiformis, Ann. Inst. Pasteur **13**: 609, 1899.

3. Smith, D. T.: Fusospirochetal Disease of the Lungs Produced with Cultures from Vincent's Angina, J. Infect. Dis. **46**: 303 (April) 1930; Relation of Vincent's Angina to Fusospirochetal Disease of the Lungs, J. A. M. A. **94**:23 (Jan. 4) 1930.

4. Lichtenberg, H. H., Werner, M., and Leuck, E. V.: The Pathogenicity of the Fusiform Bacillus and Spirillum of Plaut-Vincent, J. A. M. A. **100**:707 (March 11) 1933.

pyothorax. It is felt that diagnosis of this type of pyothorax should receive particular attention, as the treatment should be directed along lines different from the medical and surgical treatment of the more common types of pyothorax. The establishment of a diagnosis of pyothorax resulting from fusospirochetal infection may precede the proper identification of the underlying infection involving the parenchyma of the lungs and may be of great value in the true estimation of the prognosis of the case.

REPORT OF CASES

CASE 1.—Miss M. B., aged 29, was admitted to the hospital on Oct. 13, 1933. Her chief complaint was frequent cough with expectoration of moderate amounts of purulent sputum for three weeks. She had continued with her regular work as technician in a laboratory until one week before admission to the hospital, when she went to bed because of general malaise and slight fever. Twelve hours before admission she had a moderate chill, after which her temperature rose to 102 F. She had had frequent bronchial colds and a chronic cough since early childhood. She had pneumonia on three occasions between the ages of 3 and 18 years. Tonsillectomy was performed at the age of 24, at which time the patient was first treated for chronic maxillary sinusitis. Since the age of 15, she had occasionally coughed up small amounts of blood-tinged sputum, the hemorrhages occurring more frequently and increasing in volume during the previous five years. Repeated examination failed to reveal any evidence of tuberculous infection. At the age of 25 iodized poppy-seed oil 40 per cent was first used in examination of the bronchial tract, and rather extensive bilateral bronchiectasis was demonstrated. During the three years previous to the present illness the patient had expectorated from 3 to 4 ounces (88.5 to 118 cc.) of purulent sputum during the latter part of each forenoon and again during the latter part of each afternoon.

On admission to the hospital the temperature was 102 F., the pulse rate 96 and the respiratory rate 20. Examination gave essentially negative results except in the chest, in which harshness of breath sounds was noted and a few coarse, moist râles were heard over the lower half of each lung posteriorly. The leukocyte count was 21,800. The temperature remained constant at 102 F., and on the third day in the hospital a small area of dulness and pneumonic breathing was noted at the base of the right lung. The patient had a frequent harsh bronchial cough and raised small amounts of purulent sputum. Examination of the sputum revealed many pneumococci and streptococci. The temperature dropped to normal on the fifth day in the hospital, and the patient felt much better generally, the respiratory rate remaining the same. After remaining normal for two days, the temperature again became elevated, varying intermittently between 100 and 102 F. On the ninth day in the hospital the patient first complained of pain in the lower part of the chest on the right side on inspiration.

A roentgenogram of the chest showed some increased density at the base of each lung, with evidence of lobular pneumonia at the base of the right lung. The leukocyte count was 16,900. The patient continued to have moderately severe pain in the lower part of the chest on the right side on inspiration which was relieved by doses of $\frac{1}{2}$ or 1 grain (0.032 or 0.065 Gm.) of codeine. On the morning of the fourteenth day in the hospital the patient had a rather sudden onset of excruciating pain in the lower part of the chest on the right side, and general physical signs of severe shock developed rapidly. The temperature rose to 104.4 F.,

and the pulse rate was accelerated to 130, with very poor pulse volume and marked cyanosis. The respiratory rate increased to 40, with very shallow, gasping respirations. Strapping of the right side of the chest with adhesive tape eased the pain slightly. The patient was placed in an oxygen tent, whereupon the cyanosis disappeared and the temperature and pulse rate showed a decline. Frequent doses of morphine gave partial relief from the pain. The patient remained in the oxygen tent, and the immediate prognosis was considered grave because of her general weakened physical condition. There was a frequent cough, which greatly aggravated the pain in the chest.

On the twentieth day physical examination revealed some effusion in the right pleural cavity. This did not increase in amount until the twenty-fourth day, when there was evidence of a rapid increase in amount, with marked difficulty in breathing when the patient lay on the opposite side. The leukocyte count was 28,800. A roentgenogram of the chest showed complete obscuration of the right pulmonary field, with moderate displacement of the heart and mediastinum to the left. Thoracentesis was performed, and 630 cc. of thin greenish-yellow pus was aspirated from the right pleural cavity. The pus was characterized by an extremely foul odor, and on bacteriologic examination it was found to contain many pneumococci and streptococci and large numbers of fusiform bacilli and Vincent's spirilla.

Thoracotomy was considered inadvisable because of the general weakened condition of the patient and because of the very thin consistency of the empyema fluid. On the twenty-ninth day in the hospital 540 cc. of fluid was aspirated from the right pleural cavity, all the fluid being removed that could be aspirated through an 18 gage needle. On the following day a small trocar was inserted between the ribs and into the right pleural cavity, and through the trocar was inserted a small rubber catheter to which a flap valve was attached. Several ounces of pus drained from this tube, but within an hour the respirations became very shallow, the heart tones became progressively weaker, and the patient died.

Autopsy revealed evidence of pneumonia in the left lung involving the lower lobe and the apex and a moderate degree of bronchiectasis. The right lung was in complete collapse and showed marked bronchial and broncheolar dilatation throughout the lower lobe. The lower lobe contained many small bronchiectatic abscesses. These abscesses contained light green pus similar in bacteriologic characteristics to the pus aspirated from the right pleural cavity prior to death.

CASE 2.—Mr. F. M., aged 34, a sergeant in the United States Army, was admitted to the hospital on Feb. 6, 1934. He had had general malaise and pains in the lower part of the chest on the left side on inspiration five days before admission to the hospital and had been in bed for three days with moderate fever. The pains in the chest had become progressively more severe, and it was for the relief of this symptom that hospitalization was advised. The patient had had frequent "colds" for several years and since May 1930 had been treated for chronic maxillary sinusitis on numerous occasions.

On his admission to the hospital the temperature was 101 F., the pulse rate 120 and the respiratory rate 34. Examination of the nose and throat revealed moderate pharyngeal redness and a small amount of mucopurulent postnasal dripping. Expansion of the chest was diminished on the left side, and percussion revealed flatness over the left lung below the level of the sixth dorsal vertebra. Breath sounds and fremitus were absent over the area of impaired resonance. The right lung revealed no abnormalities other than some displacement of the right cardiac border to the right. Examination of the urine revealed a trace of albumin and a few pus cells. The leukocyte count was 22,200, with 80 per cent polymorphonu-

clears and 20 per cent lymphocytes. The Schilling index was 10.4. A roentgenogram of the chest showed the entire left side to be full of fluid, with considerable displacement of the heart and mediastinum to the right. No lung structure could be seen on the left side. The right lung was compressed but was normal otherwise. On the second day in the hospital thoracentesis was performed, and 900 cc. of straw-colored fluid was removed from the left pleural cavity. Examination of this fluid failed to reveal organisms, and no growth was obtained on culture. The patient had a moderately severe bronchial cough and produced small amounts of mucopurulent sputum. He complained of severe pain in the left side of the chest on inspiration and on coughing, the pain not being relieved by 1 grain doses of codeine administered hypodermically. The fever ran an intermittent course, the temperature varying from 101 to 103 F. The patient showed no respiratory embarrassment, and after the first thoracentesis physical examination failed to reveal evidence of displacement of the mediastinum. On the eighth day in the hospital the leukocyte count was 20,800. On the eleventh day a second roentgenogram of the chest showed the left side of the chest still filled completely with effusion but no displacement of the heart and mediastinum. The right lung showed no pathologic change. The leukocyte count at this time was 32,300. As the temperature was still varying between 101 and 103 F., and leukocytosis was more marked and the patient's general condition was not improving, thoracentesis was repeated on the twelfth day. The fluid, which was obtained from the left pleural cavity, was greenish-yellow pus of moderately thin consistency and with an extremely foul odor. Only a small amount of this pus was aspirated and on the fourteenth day in the hospital a thoracotomy was performed, after which large amounts of the pus drained from the cavity. Examination of this pus revealed large numbers of small bacilli morphologically similar to *Bacillus influenzae*, fusiform bacilli and Vincent's spirilla. Following the thoracotomy the fever showed a rather rapid decline, the temperature being within 1 degree of normal after the seventeenth day. However, at noon on the twenty-second day in the hospital, on getting out of bed the patient suddenly became very weak and pale. He perspired profusely and was markedly dyspneic. The pulse volume was very poor, and cyanosis developed within a few minutes. With oxygen therapy the cyanosis cleared up and the respirations became less labored. Physical examination revealed no evidence of collapse of the lung. The heart tones became progressively weaker, and the patient died one and one-half hours later.

CASE 3.—Mr. G. I., a railway official aged 52, was admitted to the hospital on March 14, 1934. His complaint was excruciating pain in the left side of the chest which was worse on inspiration. He had had a moderate "cold" with a slight cough for a week and had experienced some slight to moderately severe pain in the left side of the chest, which was worse on inspiration, during the preceding three days. He had not noted any fever and had attended to the work in his office up to the day of admission to the hospital. On that day he had awakened at 3:00 a. m. with moderately severe pain in the left side of the chest. After two hours the pain became more severe, and at 8:00 a. m. he called a physician. The physician found the patient pale, perspiring and walking the floor, being unable to stay quiet in bed because of the severe pain. The temperature was subnormal, and the pulse rate was 90. During the next two and a half hours 1 grain of morphine was given hypodermically in three doses but gave only partial relief from the pain. The patient was then taken to the hospital in an ambulance. On his admission to the hospital the temperature was 98 F., the pulse rate 110 and the respiratory rate 20. Urinalysis revealed no abnormalities. The leukocyte count was 22,700, with 94 per cent polymorphonuclears. The Schilling index was

5.7. The temperature rose to 99.6 F. during the afternoon, and the patient continued to have some pain in the left side of the chest on inspiration, requiring morphine twice during the first twenty-four hours. In the afternoon of the second day in the hospital the temperature increased to 101.8 F., with the pulse rate 110 and the respiratory rate 28. At this time pneumonic breathing was heard over the lower part of the chest on the left side in the posterior axillary line. A roentgenogram of the chest showed evidence of pleural effusion on the left side but no evidence of parenchymal abnormalities. The temperature varied from 100 to 102 F., and morphine was needed every six to twelve hours to ease the pain in the chest. A moderately frequent cough was present, but no sputum was raised. On the fourth day the leukocyte count had increased to 34,000, with 93 per cent polymorphonuclears; the Schilling index was 2.4. Physical examination revealed an effusion of the left pleural cavity filling the lower half of the chest on the left side. On the eighth day in the hospital thoracentesis was performed, and 700 cc. of moderately thin pus was removed from the left pleural cavity. The pus was light green and had a very foul odor. Bacteriologic examination of the pus revealed large numbers of fusiform bacilli and Vincent's spirilla, no other organisms being found. The patient's general condition was so poor that thoracotomy was considered inadvisable. Therefore a small rubber catheter was introduced through a trocar into the left pleural cavity through the eighth intercostal space in the posterior axillary line, and constant drainage of the empyema was established. The fluid drained freely, but the patient continued to require morphine frequently for pain in the left side of the chest. The leukocyte count on the eleventh day in the hospital was 19,800, with 81 per cent polymorphonuclears, but the temperature was higher, varying intermittently from 99 to 103 F. On the fourteenth day there was a sudden onset of severe, sharp pain in the left side of the chest, with profuse perspiration, slight cyanosis, rapid shallow breathing and a marked increase in the rate and decrease in the volume of the pulse. Physical signs indicative of pneumothorax were present over the lower portion of the left side of the chest. During the following week the patient was very weak, but the temperature was lower, the maximum never exceeding 101 F. The left pleural cavity was irrigated daily with saline solutions, and moderate quantities of thick pus drained through the catheter. The leukocyte count on the eighteenth day in the hospital was 20,600, with 69 per cent polymorphonuclears; the Schilling index was 5.3. On the twenty-second day the temperature was higher, varying from 99 to 102 F., and the leukocyte count was 23,500, with 79 per cent polymorphonuclears. On the twenty-fourth day in the hospital a roentgenogram of the chest showed a small amount of fluid in the left pleural cavity. There were marked pleural thickening on the left side and complete collapse of the left lung. No pathologic change was noted on the right side. It was thought that drainage of the left pleural cavity was unsatisfactory owing to the thick consistency of some of the purulent exudate and the small caliber of the intercostal drain. The patient had shown a slow increase in strength following the development of the pneumothorax, and on the twenty-seventh day thoracotomy was performed with no untoward reaction. Satisfactory drainage was established, and the temperature showed a slow decline until it reached normal on the fifty-second day. The leukocyte count was 22,750 on the forty-third day and had decreased to 12,250 on the fifty-eighth day. The amount of drainage of empyema fluid gradually decreased and was very slight at the time the patient was discharged on the sixty-eighth day after he was admitted to the hospital.

The administration of neoarsphenamine intravenously was started the day after the thoracentesis was performed which established the diagnosis of empyema caused

by fusospirochetal infection. Five doses of 0.3 Gm. each were given at intervals of from seven to ten days during the remainder of the patient's stay in the hospital. One dose was given two weeks after he was discharged.

Eight days after the patient was discharged from the hospital a roentgenogram of the chest showed a rather large pneumothorax on the left side with a small amount of effusion at the base of the lung. The right lung appeared normal. At this time the leukocyte count was 13,600, with 70 per cent polymorphonuclears; the Schilling index was 10.7.

The patient was last seen eight weeks after discharge from the hospital, at which time a very small amount of pus was draining from the thoracotomy opening. The leukocyte count was 11,000. The patient was taking a moderate amount of physical exercise and was feeling well.

COMMENT

In two of this series of three cases definite evidence of infection involving the parenchyma of the lungs was present prior to the development of pyothorax. It is believed that the fusospirochetal infection was secondary, first in the parenchyma of the lung and later in the pleura.

I have not observed inspiratory thoracic pain of such severity in other types of pulmonary infection, and in no other cases have I observed the persistence of the pain long after the development of pleural effusion. The persistence of severe pleural pain after the development of effusion should make one suspect the presence of fusospirochetal infection.

In all the cases of this series the pus drained from the pyothorax possessed a very foul, fetid odor. In none of the cases did the sputum possess this odor, nor was the breath fetid. It is believed that a localized area of pulmonary gangrene developed prior to the development of the pyothorax. In cases 1 and 3 it is believed that the occurrence of spontaneous pneumothorax aided materially in the control of the acute infection involving the parenchyma of the lung.

Marked leukocytosis was observed in all the cases, the maximum count varying from 28,800 to 34,000.

In all the cases reported oral hygiene had been good. In case 1 there was a chronic bronchiectatic condition, and in case 2 chronic maxillary sinusitis was present, and it is presumed that in both cases fusospirochetal organisms were present in the respiratory tract. In case 3 there were no history and no physical evidence of oral infection or infection of the upper respiratory tract prior to the onset of the illness reported.

In two of the cases the general condition of the patient was so grave that following the establishment of the diagnosis of pyothorax thoracotomy was considered inadvisable. In these cases an intercostal drain was installed, and thoracotomy was performed later, at a time when the patient's condition had improved. It is believed that such conservative treatment is justified.

In only one case was arsenic therapy used. In case 3 neoarsphenamine was administered intravenously at regular intervals from the time of the diagnosis of fusospirochetal infection throughout the acute stage of the infection. It is believed that neoarsphenamine should be administered intravenously at regular intervals in every case of acute fusospirochetal infection.

SUMMARY

Three cases of acute pulmonary disease with pyothorax due to fusospirochetal infection are reported.

The diagnosis was established only after the presence of fusospirochetal organisms in the empyema fluid was observed.

Attention is called to the severity of the pleural pain and to the fact that the pain persists after the development of pleural effusion.

The fetid odor of the pus obtained from the pyothorax in this type of infection is considered of diagnostic importance.

It is believed that this type of acute pulmonary infection is much more common than a survey of the medical literature would indicate, and a plea is made for more consideration of this type of infection in the differential diagnosis of cases of acute pulmonary disease.

Progress in Internal Medicine

GASTRO-ENTEROLOGY IN 1934

GARNETT CHENEY, M.D.

SAN FRANCISCO

In surveying the literature on gastro-enterology for 1934 it has been my aim to present abstracts of only those articles which might be of interest and of practical value to the general practitioners of medicine who are familiar with the wide variety of gastro-intestinal disorders. In following such a plan, certain textbook subjects, such as cancer of the stomach and appendicitis, concerning which the usual large number of articles have appeared, have been discussed but briefly, because practically nothing new has been written about them. As some diseases have been given considerable attention and others none, the consequence is an unbalanced review of the very extensive field of gastro-enterology. But it is hoped that the elimination of reports on subjects which contribute little or nothing to the advancement of the knowledge but are often included for the sake of completeness will give the reader a clearer and more concise insight into the progress made in this field during the past year.

ESOPHAGUS

Under the heading "Some Disorders of the Esophagus," Hurst¹ describes four syndromes which he considers relatively new and not uncommon. He believes that every physician has encountered them and will be better able to recognize them in the future. The first of these he terms dysphagia of anemic women. There is anemia of the hypochromic type, often associated with deficient gastric acidity and occasionally with splenomegaly. Atrophic glossitis is constantly present, which is identical in every respect with the glossitis of pernicious anemia described by Hunter. Hurst believes that the dysphagia is a result of a disturbance in the neuromuscular mechanism, causing relaxation of the normally closed pharyngo-esophageal sphincter. He designates this achalasia and says that it is caused by a spread of the atrophic inflammation of the mucous membranes in the neighborhood to involve either the nerve endings or the ganglion cells of Auerbach's plexus, which control the sphincter. There is no pathologic proof of such an etiology.

1. Hurst, A. F.: Some Disorders of the Esophagus, J. A. M. A. **102**:582 (Feb. 24) 1934.

The anemia responds rapidly to the administration of iron, and the dysphagia can be cured by the passage of bougies weighted with mercury.

The syndrome actually differs from simple achlorhydric anemia only by the presence of the complicating dysphagia. Hurst points out that the name Plummer-Vinson's syndrome, which he gave it in 1926, is not justifiable, as it was first described by Kelly and by Paterson in 1919.

The second syndrome described is not new, but Hurst's interpretation of the underlying cause gives a new conception of a well recognized condition. He describes so-called cardiospasm as achalasia of the cardiac sphincter. The enormous dilatation and hypertrophy of the esophagus, thought to be due to spasm of the cardiac sphincter, are in reality due to a loss of proper relaxation of the sphincter, or achalasia. Convincing evidence is presented that this assumption is correct and that the etiology is chronic inflammation of Auerbach's plexus in this region, which causes a lack of the normal relaxation response of the sphincter. Dilatation by the mercury tube effects a cure in the large majority of cases. If operation is necessary, the procedure of choice is stretching the sphincter from below by introducing the fingers through the stomach. An interesting and historic report of a case by Thomas Willis, published in 1672, is included, which presents the theory of achalasia as opposed to that of cardiospasm.

The third syndrome is that of chronic peptic ulcer of the esophagus. As this has been more adequately described in a separate article, it will be reviewed subsequently. The fourth syndrome has been designated the recurrent hiatus syndrome of von Bergmann. The tissues around the hiatus oesophageus must be abnormally lax so as to permit the formation of a diaphragmatic hernia. This may be congenital, but the preponderance of its occurrence in elderly persons suggests that it is not. It is to be clearly differentiated from the familiar type of non-traumatic diaphragmatic hernia which results from congenital shortness of the esophagus. The hernia is generally intermittent, being produced by increased intra-abdominal pressure. Characteristically the hernia occurs when the patient bends over or lies prone. It may produce a variety of symptoms, the chief of which seems to be intermittent pain or pressure under the xiphisternum, usually nocturnal at the onset. Vomiting is sometimes the only symptom. An attack is relieved when the patient sits up or stands or when the stomach is distended with an aerated drink. The technic of the roentgen examination is of the utmost importance. The hernia ordinarily can be demonstrated only while the patient is lying down, and the barium sulphate meal should be administered with the patient on his back. When the patient stands up, the hernia disappears. Only a clinical knowledge of the manifestations of

recurrent hernia of the hiatus will lead to the special type of roentgen examination necessary to disclose this rare form of herniation. Treatment must be directed to the avoidance of anything that is likely to increase intra-abdominal pressure.

Cunha² reports 2 cases of the recurrent "hiatus hernia" syndrome of von Bergmann and stresses the symptomatology and the treatment. Reproductions of the roentgenograms showing the hernias are included, with the notation that they were taken with the patient in the recumbent position and that the hernia of the hiatus could not be visualized with the patient in the upright position. The symptoms may resemble those of ulcer or disease of the gallbladder. The most prominent symptom is substernal distress or pressure, and dysphagia may be experienced. In Cunha's cases the complaint was of food passing up and down the esophagus and seemingly not entering the stomach. Pain is often substernal or sharply localized in the midportion of the epigastrium and may be referred through to the back. Nocturnal distress while the patient is lying in bed with relief when the patient sits erect is frequent. Inflammation of the involved area and ulceration of the lower end of the esophagus may occur. On roentgen examination, repeated observations may be required to demonstrate the lesion; having the patient carry on forced deep inspiration may be of distinct aid in visualization of the hernia. The treatment outlined is largely symptomatic. The avoidance of both external and internal factors which may lead to an increase of intra-abdominal pressure is emphasized.

Under the heading "Thoracic Stomach," Goodall and Hoyt³ report 5 cases of congenitally short esophagus, with a part or all of the stomach above the diaphragm. The condition in these cases is to be carefully distinguished from true hernia of the diaphragm and from the protrusion of small portions of the stomach through the esophageal opening of the diaphragm when the esophagus is of normal length. The authors could find reports of only 7 similar cases in the literature, although they believe that a good many cases reported as instances of hernia of the diaphragm were probably cases of congenitally short esophagus with thoracic stomach. An exact diagnosis must depend on detailed roentgen studies.

The symptoms of thoracic stomach are due to: (1) interference with normal peristalsis of the gastro-intestinal tract and (2) embarrassment of the thoracic organs. The symptoms may arise in early life and persist until death. Cardiorespiratory symptoms predominate when the greater part of the stomach is above the diaphragm, and they have a

2. Cunha, F.: Recurrent "Hiatus Hernia" Syndrome of von Bergmann, *Am. J. Digest. Dis. & Nutrition* 1:170, 1934.

3. Goodall, H. W., and Hoyt, L. H.: Thoracic Stomach: Report of Five Cases, *Arch. Int. Med.* 53:594 (April) 1934.

tendency to appear late in life. Dyspnea on ordinary activity is a characteristic finding. It rapidly disappears when the patient is at rest. A sense of substernal fullness is common if the patient overeats and is immediately relieved by vomiting. The real digestive symptoms are those of persistent hyperacidity, and they may be complicated by the presence of an ulcer. Attacks of abdominal pain, nausea and vomiting may occur. Anemia occurred in 1 case, but a duodenal ulcer was found on postmortem examination.

The problem of treatment belongs to the field of the internist and not to that of the surgeon, for the short esophagus cannot be corrected. Therapy is, for the most part, dietary, and a complete regimen similar to that instituted in cases of peptic ulcer may be necessary.

Chronic peptic ulcer of the esophagus is rare. Hurst⁴ reports 3 more cases to be added to the literature, in 2 of which the ulcer was demonstrated by roentgen examination. Usually this lesion can be diagnosed only by esophagosopic examination. Discomfort or pain occurs under the lower end of the sternum while solid food is being eaten or, less frequently, half an hour or more after meals. It often radiates to the back. At first, pain is not caused by the ingestion of soft foods and liquids, lasts only a few minutes and is relieved by alkalis. Later, the pain is prolonged and is followed by regurgitation. The patient is afraid to eat. Severe hematemesis, perforation or obstruction may occur. An esophageal ulcer has all the anatomic characteristics of a chronic ulcer of the stomach or duodenum. It always occurs just above the cardiac sphincter, apparently in an area of heterotopic gastric mucous membrane. The treatment is similar to that given in cases of peptic ulcers which occur elsewhere. Obstruction may require gastrostomy.

STOMACH

Gastric Physiology.—The study of gastric physiology seems to attract the attention of an ever increasing number of investigators. Most of the knowledge of the functions of the stomach can be traced to laboratory experimentation on animals and on man, and much that is of interest and of promise in the field of gastro-enterostomy has been published by research workers. It behooves the internist to try to keep pace with the physiologist and apply the latter's knowledge to the practice of medicine. With this in mind, a few papers dealing with a number of different problems in gastric physiology have been included in this review.

Experimental data concerning the influence of the sympathetic nervous system on the secretory activity of the stomach are scarce and

4. Hurst, A. F.: Chronic Peptic Ulcer of Esophagus, *Guy's Hosp. Rep.* **84**: 104, 1934.

CHENEY—GASTRO-ENTEROLOGY

controversial. Although the results of Baxter's investigations⁵ in this field on dogs and cats cannot necessarily be applied in their entirety to man they are of particular interest because of their bearing on the rationale of mucin therapy of peptic ulcers and because of the possible effects on gastric secretion of splanchnectomy for high blood pressure. It has been stated that sympathetic fibers may both excite and inhibit gastric secretion and that their effect on the fundus of the stomach may differ from that on the pylorus, particularly as regards the secretion of mucus. There are also differences of opinion as to the influence of epinephrine on secretion. Baxter has devised a number of complicated operations on animals in an effort to solve these problems. He concludes from his experiments that long continued rhythmic stimulation of the splanchnic nerves produces a steady secretion of alkaline mucus possessing a low digestive power. Repeated injections of epinephrine had a similar effect. The "paralytic secretion" of alkaline mucus which follows the section of the splanchnic nerves probably depends on an altered vascularization of the stomach. All parts of the stomach secrete mucus, the pylorus being the chief source of secretion, the body of the stomach serving as a less prolific source and the fundus contributing very little. A weak stimulation of the vagus nerve also produces a secretion of mucus from the stomach of the dog and of the cat. Further experiments have established the fact that the sympathetic nervous system does not play an essential part in the first, or nervous, phase of gastric secretion. It has long been known that this phase is mediated chiefly by the parasympathetic nervous system.

For a number of years Hollander⁶ has been studying the physiology of gastric secretion. In a recent article, "The Composition of Pure Gastric Juice," he reviews the results of much previous experimental work in this field and endeavors to correlate them with more recent observations. Of particular interest is the precise quantitative evidence he offers of the constant acidity of gastric juice as it flows from the glands. This is in accord with Pavlov's theory and contrary to the Rosemann theory of variable acidity of the parietal secretion, in which the acidity is integrally related to the rate of its formation. It seems probable that Hollander's studies have settled this controversial problem, although in the absence of reliable information concerning the composition of the alkaline component of gastric secretion the final word on constant acidity may not yet have been said.

5. Baxter, S. G.: Sympathetic Secretory Innervation of the Gastric Mucosa, *Am. J. Digest. Dis. & Nutrition* 1:36, 1934; Role of the Sympathetic Nervous System in Gastric Secretion, *ibid.* 1:40, 1934.

6. Hollander, F.: The Composition of Pure Gastric Juice, *Am. J. Digest. Dis. & Nutrition* 1:319, 1934.

Gianturco,⁷ working at the Mayo Foundation, has carried out a new type of experimental study on the mechanics of gastric activity. He used trained cats as experimental animals, as their stomachs are strikingly similar to the stomach of man. Most of the experiments were carried out by means of roentgen rays, the usual form of contrast mediums being utilized. In order to observe the movements of the visceral walls themselves, small chilled lead shot was placed under the serosal coat of the stomach. A month after the operation the cats were ready for roentgenographic examination, and records were made on roentgen cinematographic films.

While studying the empty stomach and its various ways of filling, it was first noted that in nine fasting animals with the shot in place, hunger contractions could not be observed. This was not in accord with the evidence of pronounced peristalsis observed when a balloon is inserted into the stomach and inflated, and it suggested that the so-called hunger contractions are caused by distention of the stomach by the recording balloon. In a further similar experiment, after serial roentgenograms were made, shallow peristaltic contractions animating the empty stomach were evident. The theory that food entering the stomach follows closely the lesser curvature, the *Magenstrasse*, was, in the main, disproved. When barium, fluids and food entered the cat's empty stomach, they were carried toward the pylorus by peristaltic waves without following the *Magenstrasse*. This pathway was followed only when small amounts of material entered a stomach already filled with solid food.

In considering the pressure exerted by the gastric walls, it was found that because of active gastric relaxation of the fundus and body of the stomach the intragastric pressure does not change until a large amount of material has been introduced. The rise in pressure which follows further filling is largely the result of stretching of the abdominal walls. Feeding cats large pieces of meat coated with powdered barium enabled Gianturco to follow the physical changes occurring to the foodstuff during digestion and to study the process of liquefaction during the whole course of digestion.

The pyloric mechanism was studied in cats in a similar manner, except that shot was placed also in the walls of the pylorus and duodenum, so that peristaltic waves could be followed on both sides of the sphincter. Although the theory of acid control of the pylorus has been disproved, none of the investigators have ever been able to record simultaneously all the mechanical factors that determine the passage of gastric contents into the duodenum. Cinematographic roentgenograms

7. Gianturco, C.: Some Mechanical Factors of Gastric Physiology, Am. J. Roentgenol. **31**:735 and 745, 1934.

CHENEY—GASTRO-ENTEROLOGY

of the prepared cats made it possible to make records of every phase of gastric activity. From these pictures Gianturco concludes that the pylorus responds to approaching waves of peristalsis much as does the adjacent region of the pars pylorica. Food leaves the stomach when the pylorus and the duodenum are relaxed at the same time. Relaxation of the pylorus alone is not followed by the passage of food.

The effect of various foods on the emptying of the stomach was also studied. The various substances fed were mixed with barium, and their course through the stomach was followed with the roentgenoscope. It was found that the emptying time for different foodstuffs depends, first, on the physical state and, second, on the chemical nature of the substance. Fats and hypertonic solutions of salt or sugar were most conspicuous in slowing gastric evacuation, and this action was apparently the result of marked changes in the activity of the walls of the stomach and of the duodenum, which occurred even after removal of the pyloric ring and after gastro-enterostomy.

Quigley⁸ commences his article on "Natural Chemical Factors Governing Gastric-Motility" with this statement: "A thorough appreciation of gastro-intestinal physiology is a prime requisite of a gastro-enterologist." Although the motility of the intestine has been ascribed predominantly to nervous mechanisms, actually humoral control may play an important part. The particular problem attacked by the author is how the ingestion of carbohydrates or fats decreases gastric motility and depresses hunger. By means of the balloon method and a series of carefully planned operations on dogs, Quigley showed that these effects are not dependent on the nervous system. In denervated stomachs, fats and sugars led to gastric inhibition similar to that which occurs in normal stomachs. The administration of large doses of secretin and cholecystokinin did not inhibit gastric motility. The motility of the pouch of an entire stomach was not inhibited when fat and carbohydrates were introduced into it; but it was inhibited when fat and carbohydrates were introduced into the duodenum, even when the blood vessels of the stomach had been stripped and phenolized.

Quigley concludes that since nerve reflexes were precluded, the hydrates liberate humoral factors from the mucosa of the upper intestine which resemble an inhibitory hormone. Hunger would terminate, and the inhibition of gastric digestive contractions would retard, the entrance of gastric contents into the duodenum. Such a mechanism might tend to prevent overloading of the stomach and, more especially, the intestine.

8. Quigley, J. P.: Natural Chemical Factors Governing Gastric-Motility, *Am. J. Digest. Dis. & Nutrition* 1:425, 1934.

The problem of the mechanism of pyloric function has been the incentive for a long series of investigations, the results of which have been controversial. Cannon's early theory of "the acid control of the pylorus" has been proved incorrect, as Ivy found that strong acids in the duodenum most frequently cause relaxation of the sphincter and regurgitation of duodenal contents into the stomach. Ryle decided that the important factors promoting pathologic hyperacidity are excessive gastric acidity and pyloric hypertonicity. It has long been suggested that gastric acidity in man is controlled by the regurgitation of alkaline duodenal contents into the stomach, but definite proof has been lacking. The importance of the relation of such a mechanism to the high range of acidity usually encountered in cases of peptic ulcer is obvious. Lehrmann and Nelson⁹ have utilized a new approach to this problem and have based their observations on a series of cases of duodenal ulcer occurring in man. They modified a Rehfuß tube for gastroduodenal studies by inserting a metal bar dividing the perforated tip horizontally into two parts, which would lie in the stomach. The distal half was connected with a short piece of tubing ending in the usual Rehfuß bulb, which would lie in the duodenum. When the complete gastroduodenal tube was in place (which was always verified by fluoroscopic examination) the pylorus could not close, free regurgitation of duodenal contents could take place into the stomach, and the contents would mix with the gastric secretion. Ordinary fractional analysis of the gastric contents could be carried out by removing specimens through the proximal portion of the tube. It was found that regurgitation of bile and trypsin was very noticeable in all specimens examined during the gastroduodenal tests in 12 cases of duodenal ulcer, although these constituents had been absent in most of the fractional gastric analyses previously made on these patients. Lehrmann's and Nelson's findings lend support to the work of others concerning the dominant part played in gastric function by the pylorus and the duodenum, but of perhaps greater interest to the clinician are the changes in the acid curves noted in these studies. The graphs clearly show that the hyperacidity present on fractional gastric analysis no longer exists during gastroduodenal studies on the same patients when the pylorus is maintained patent. In the latter event the acid curve reaches its peak, approximately a normal figure, within an hour and subsequently drops. Here is convincing proof that free regurgitation of duodenal contents, which is naturally controlled by the tonicity of the pyloric sphincter, plays a part in the "chemical control" of gastric secretion and that pylorospasm is primarily responsible for the hyperacidity so characteristic of peptic ulcer.

9. Lehrmann, W. W., and Nelson, T. M.: The Influence of the Pylorus upon the Regulation of the Acidity of Gastric Secretion, *Am. J. Digest. Dis. & Nutrition* 1:245, 1934.

CHENEY—GASTRO-ENTEROLOGY

A comparison of intragastric and duodenal factors in lowering the acidity of gastric contents has been made by Wilhelmj, Neigus and Hill.¹⁰ A brief review of the controversial literature on this subject is presented, and a number of experiments on dogs are recorded. The important findings are: 1. Ligation of the bile and pancreatic ducts resulted in slowed and incomplete reduction of acid solutions placed in the stomach. 2. With a free flow of acid in the intact normal stomach, it was possible to separate the secretion into two parts, the first containing unneutralized hydrochloric acid and the second, or extra fluid, composed of neutralized hydrochloric acid and pyloric and regurgitated duodenal secretions. 3. In the whole stomach there was a direct relationship between the amounts of extra fluid, neutral chloride, bile and acid deficit. 4. Pyloric and duodenal secretions reduced acidity more by dilution than by neutralization. The duodenal contents are more efficient in this respect because more are available.

Daikhovsky and Solovei,¹¹ in a paper entitled "Clinico-Experimental Observations of Excretory Function of the Stomach," report the excretion time of neutral red in 45 patients with gastro-intestinal disorders. Although a great deal of work has already been done with gastric chromoscopic examination, the authors' observations suggest a new field for this test as a practical medical procedure. They found that the excretory function of the stomach may be upset when there is no disturbance of secretion. From experimentation on animals as well as from an analysis of clinical material, it is evident that the secretion of hydrochloric acid is primarily a function of the mucous membrane of the fundus of the stomach and that the excretion of neutral red is a function of the mucous membrane of the pyloric portion. As these two functions may not correspond, it might be possible to detect pyloric lesions interfering with excretion of the dye even when adequate amounts of free hydrochloric acid were being secreted. Daikhovsky and Solovei found this to be true clinically in the presence of inflammatory changes in the gastric antrum, such as gastritis with or without peptic ulcer and gastroduodenitis, and were able to correlate the chromoscopic findings with changes in the relief of the stomach as determined roentgenologically. They deduce from these observations that retardation or absence of the secretion of neutral red by the gastric mucosa indicates inflammatory changes in the antrum of the stomach and that a test of secretion of neutral red offers a valuable method for the early detection of antral gastritis.

10. Wilhelmj, C. M.; Neigus, I., and Hill, F. C.: Comparison of Intragastric and Duodenal Factors in Lowering Acidity of Gastric Contents, *Am. J. Physiol.* **107**:490, 1934.

11. Daikhovsky, J. I., and Solovei, M. G.: Clinico-Experimental Observations of Excretory Function of Stomach, *Acta med. Scandinav.* **83**:79, 1934.

The relationship between many gastro-intestinal disorders and the underlying cause of certain types of anemia is growing closer and closer. A keen student of gastro-enterology must be a close student of hematology. Many of the contributions to these two broad fields of medicine so overlap that any review of gastro-intestinal disorders must reserve a section for recent advances which might be properly placed in either field. A subject which has commanded a great deal of clinical attention and has stimulated an immense amount of experimental work is the relationship of gastric function to anemia. Only a few of the most pertinent articles are reviewed.

Ivy and his co-workers¹² have studied the relationship of gastrectomy to anemia in the dog and the presence of the substances effective in the treatment of pernicious anemia in the canine stomach and liver. Dogs deprived of their stomachs do not show the blood picture of pernicious anemia but rather that of hypochromic anemia, which responds to suitable iron therapy and does not respond to the administration of the liver extract fraction G from a patient with primary anemia. Rats and pigs on which gastrectomy has been performed show the same form of anemia. The primary defect seems to be one of absorption of iron. Canine desiccated stomach and canine liver are effective in the treatment of pernicious anemia in man but are of low potency in comparison to bovine stomach and liver. These observations lead the authors to question whether a lack of the intrinsic gastric factor of Castle can be the primary cause of pernicious anemia. They suggest that this unknown substance may also be present in the intestine, or that other factors are concerned in the etiology of this disorder.

Although macrocytic anemia resembling pernicious anemia has not been constantly produced in dogs and swine and in man by gastrectomy, Miller and Rhoads¹³ produced this type of anemia in swine given a deficient diet. A characteristic symptom complex developed with a diet which causes canine black tongue and which is deficient in those anti-anemic factors which are necessary to the successful treatment of pernicious anemia. Macrocytic anemia, lesions of the oral mucous membranes, gastric achlorhydria, diarrhea and motor weakness of the extremities were the principal manifestations. Changes in the bone marrow characteristic of pernicious anemia also occurred. When the disease was present, it was impossible to demonstrate hematopoietic activity of the gastric secretion or liver when tested on human beings

12. Ivy, A. C.; Richter, O.; Meyer, A. F., and Greengard, H.: Relation of Gastrectomy to Anemia; Presence of Substances Effective in Pernicious Anemia in Canine Stomach and Liver, *Am. J. Digest. Dis. & Nutrition* **1**:116, 1934.

13. Miller, D. K., and Rhoads, C. P.: The Experimental Production of Loss of Hematopoietic Elements of the Gastric Secretion and of the Liver in Swine with Achlorhydria and Anemia, *J. Clin. Investigation* **14**:153, 1935.

with pernicious anemia. The macrocytic anemia in swine responded to liver therapy just as in human patients. Miller and Rhoads are the first to produce a syndrome of pernicious anemia in experimental animals, and it is noteworthy that it was accomplished by dietary measures and that the gastric achlorhydria occurred secondarily.

Dedichen¹⁴ has studied the changes of the blood in 164 patients who had previously been subjected to gastric resection. Anemia developed in just over 50 per cent, which is a higher incidence than occurs in "spontaneous" achylia. Only 27 per cent of the men were affected, while 82 per cent of the women became anemic. All but 1 of 34 women under 40 were anemic. In most cases the anemia was of the secondary type, with a low color index, but the cases of 2 patients with the characteristics of pernicious anemia are described in detail. The author believes that achylia cannot be solely responsible for the changes of the blood, particularly since some of his patients with anemia showed free hydrochloric acid despite gastric resection.

Larsen¹⁵ has also studied the blood of a group of patients on whom gastrectomy had been performed and, in addition, patients on whom gastro-enterostomy had been performed. The chief value of his report is that his observations were made on an average of about twelve and one-half years after the operation. Of 35 women whose stomachs had been resected, he found 17 with anemia (hemoglobin content less than 80), and of 51 men, 14 had anemia (hemoglobin content less than 90). Of 26 women on whom gastro-enterostomy had been performed, 9 had anemia. Only 10 men of the group of 39 had anemia following the same operation. Only 1 case of typical pernicious anemia was noted, despite the long postoperative period. Larsen's figures correspond to the majority reported in the literature and are similar to those of Dedichen.

Gastritis.—The question of gastritis is receiving a great deal of attention and is mentioned elsewhere in this review in intimate connection with other subjects. Most of the recent studies are recorded in the foreign literature; they have been largely advanced clinically by the introduction of a flexible gastroscope and by the development of a special technic in examining the gastric mucosa roentgenologically. Although a good deal of new and stimulating information has been presented, these highly specialized methods of studying a patient with a stomachache are not yet available to the average internist or even to the clinic of the average hospital. One is almost led to believe that a superroentgenologist on the right hand and a gastroscope in the left

14. Dedichen, J.: On Blood-Changes After Gastric Resection, *Acta chir. Scandinav.* **75**:242, 1934.

15. Larsen, T. H.: On Presence of Anemia After Ventricle Operations, *Acta med. Scandinav.* **83**:110, 1934.

hand are necessary additions to the investigation of gastric disorders. Undoubtedly for practical purposes these specialized investigations are required in a small number of cases; just how small a number remains to be seen. It is possible that certain severe forms of gastritis are not as common in the United States as abroad, just as large indurated gastric ulcers are not as common here. Of particular interest as regards the study of gastric inflammation is the increasing mass of evidence gathered from different sources that gastritis, often termed antral gastritis, precedes the formation of peptic ulcers of the stomach.

The most complete and up-to-date description of gastritis is given in Henning's book on inflammation of the stomach, published in Germany. It is reviewed by Kalk.¹⁶ All forms of acute and chronic gastritis are discussed in detail and in the light of the most recently acquired knowledge made available by roentgen and gastroscopic examination. The importance of the gastroscope is strongly emphasized, and every phase of its usefulness is described. Practically everything worth knowing on the subject is made available in Henning's excellent work.

Henning discusses the problem of gastritis more briefly, though thoroughly, in the *Medizinische Klinik*.¹⁷ The known etiologic causes of inflammation of the stomach are mechanical and chemical injuries to the mucous membrane, outspoken infections and possibly occult infections. There is much to suggest peptic digestion as a primary cause, but this is not yet completely proved in man. The symptoms are not necessarily specific, but pain similar to that of the pyloric syndrome is common and may resemble that of peptic ulcer of short duration. In many cases of severe gastritis the condition cannot be diagnosed by roentgen examination, and only gastroscopic study will give conclusive evidence of inflammation. Gastric analysis usually reveals diminished acidity, and excessive amounts of mucus may or may not be present. The *Trockendiagnostik* (to be described later) is a simple and valuable diagnostic aid.

In many cases the condition clears up when the underlying cause is relieved, such as circulatory failure and known infectious diseases. In cases of doubtful etiology it is most important to remove any focus of infection. In the many cases of unproved etiology, symptomatic therapy must be instituted. Details of gastric lavage, the administration of drugs, substitution therapy, such as the administration of dilute hydrochloric acid, pepsin and mucin and a dietary regimen are all presented in a practical manner. Many patients rapidly improve on such a regimen. Roentgenologic and endoscopic examination should not be delayed in chronic cases but must be carried out by specialists.

16. Kalk, H.: Gastritis, Deutsche med. Wchnschr. 60:236 and 276, 1934.

17. Henning, N.: Ueber Gastritisprobleme, Med. Klin. 30:1151, 1934.

Observations of a dried drop of gastric juice have been made to distinguish between the secretion of a normal stomach and the secretion of an inflamed stomach. The drop from a stomach with gastritis shows a peripheral transparent laked area at the circumference, which has been termed the *Ringphänomen*, which does not normally appear and is caused by the increased protein content of the gastric secretion. Henning and Norpoth¹⁸ have carried on further experimental observations on the microscopic picture of dry gastric juice.

The dry residuum of a drop of pure gastric secretion shows a lattice work pattern of crystals of sodium chloride, which differs in its appearance when saliva or duodenal contents are added. These changes are well illustrated, and the characteristics of pure gastric juice are quite different from mixtures with other secretions. Henning and Norpoth also added small amounts of blood serum to a drop of pure gastric juice, producing the clear Ring zone which is characteristic of increased protein concentration.

One of the first reports on the use of the new Wolf-Schindler flexible gastroscope in this country is by Benedict,¹⁹ working at the Massachusetts General Hospital. In his introduction he states that the first gastroscopic examination was performed in 1868 by Küssmaul, whose subject was a professional sword swallower. Most of Benedict's 75 patients "did not find gastroscopy a severe ordeal; in fact, one patient slept throughout the examination." The author believes that direct inspection of the mucous membrane of the stomach is a valuable adjunct to roentgen studies in the diagnosis of gastric disorders. The lining of a normal stomach is described and illustrated before Benedict passes on to the findings in the stomachs of persons with gastritis. The stomachs of 22 patients with inflammation of the wall of the stomach were observed, and redness, swelling, tortuous rugae and, in some cases, erosions and small hemorrhages were readily discerned. Edematous areas, with collections of mucopurulent material characteristic of hypertrophic gastritis, were seen. Histories of cases in which gastroscopic study was of paramount importance in establishing a correct diagnosis are included, and the history of the simulation of ulcer by gastritis is emphasized. Gastric ulcer is easily visualized; and the course of healing is followed even more accurately by gastroscopic study than by roentgen examination. At times, a benign ulcer may be distinguished from a malignant ulcer on its appearance alone. There were no cases of gastrojejunal ulcer in this series. In 2 of 12 cases of gastric tumor the

18. Henning, N., and Norpoth, L.: Experimentelle Untersuchungen über das mikroskopische Bild des eingetrockneten Magensaftes, Arch. f. Verdauungskr. 55: 35, 1934.

19. Benedict, E. B.: Examination of the Stomach by Means of a Flexible Gastroscope: A Preliminary Report, New England J. Med. 210:669, 1934.

tumor was overlooked on gastroscopic examination but in another case a tumor was observed which was not found on roentgen examination.

The author concludes that examination by means of the flexible gastroscope is an easy, harmless and profitable procedure. The greatest field of usefulness is in cases of gastritis, but it is also useful as an adjunct to roentgen study of other conditions.

Peptic Ulcer.—Hanke²⁰ has studied the experimental production of acute gastric ulcers in cats by means of repeated injections of insulin. He administered a series of doses until the animal died, usually within thirteen hours, with signs of hypoglycemic shock similar to those occurring in man. No constant observations as regards gastric motility were made post mortem, although in most instances the pylorus was markedly contracted and the cardia relaxed. The gastric secretion was significantly increased and was high in acid content. Grossly and microscopically the stomachs showed the formation of acute ulcers and erosions, which extended into the lower end of the esophagus and into the upper portion of the duodenum. The mucous membrane was markedly inflamed, especially in the pyloric region, the epithelial surface being extensively involved, with definite extension into the deeper layers. Hanke has termed the condition acute hormonal gastritis, comparable to that found in similar experiments using morphine, pilocarpine and caffeine instead of insulin.

The interpretation of these results is that the hormone insulin stimulates an extensive secretion of gastric juice rich in acid and pepsin and that gastritis is a result of their surface digestive action. This process goes on to areas of fibrinous necrosis with acute inflammatory leukocytic infiltrations. Such a "peptic gastritis" may be an early stage in the formation of peptic ulcer in man. Toxins and pyloric spasm may predispose to a similar form of gastritis.

Gastric ulcers associated with cinchophen poisoning were unknown before 1932. In that year a typical chronic ulcer of the stomach and duodenum developed in a number of dogs receiving large doses of this drug. In the same year a case was reported in man. Block and Rosenberg²¹ report the second case and consider the possible etiologic relationship. The chronic gastric ulcers of their patient were unusual in their irregular oval formation and in their location at the cardia. The patient had taken mono-iodocinchophen on and off for three years, during which time gastro-intestinal symptoms developed. She died shortly after profuse hematemesis.

20. Hanke, H.: Experimentelle Untersuchungen über hormonale Ulcuserzeugung; die akute erosive Insulin-gastritis und ihre Pathogenese, *Ztschr. f. d. ges. exper. Med.* **94**:405, 1934.

21. Block, L., and Rosenberg, D. H.: Gastric Ulcers Associated with Cinchophen Poisoning, *Am. J. Digest. Dis. & Nutrition* **1**:29, 1934.

A number of papers have appeared on recently introduced methods of medical treatment of chronic peptic ulcer of the stomach and duodenum. This search for better methods of therapy in this field not only denotes a sustained interest in the problem but suggests that the generally utilized dietary and alkali management developed in the early part of this century is not altogether satisfactory. A few of the newer methods of treatment are based on sound physiologic principles; many seem to be based more on theory than on fact. For the sake of completeness all have been more or less briefly reviewed. It does not appear that any of them will replace the long established Sippy type of regimen, but some of them may prove a helpful adjunct to this form of therapy, and some may prove valuable in cases in which the condition is otherwise refractive.

Treatment of peptic ulcer with gastric mucin was first reported five years ago and has been widely taken up since. The clinical results in 555 cases studied by questionnaires issued by the Gastric Mucin Committee of the Northwestern University Medical School have been published by Fogelson.²² The gastric mucin dispensed for treatment has had to meet rigid requirements of standardization by the committee since 1931. The conclusions are: 1. Of 494 patients with peptic ulcer treated throughout the United States, all symptoms were controlled in 70.5 per cent, partial relief was obtained in 23 per cent, and failure occurred in 6.5 per cent. 2. Of 217 patients with intractable ulcers, 69 of whom had submitted to previous surgical procedures, gastric mucin afforded complete relief in 63.1 per cent, partial relief in 29.4 per cent and no relief in 7.5 per cent. 3. The results in this group of patients with intractable ulcer suggest the possibility of obtaining symptomatic relief with gastric mucin when accepted orthodox measures have failed. 4. The permanence of the results is not considered, because of the limited period of observation.

The use of mucin in the treatment of peptic ulcer has stimulated a series of investigations into the properties of this substance which would justify its clinical use on a sound physiologic basis. In a number of carefully controlled experiments on the effect of mucin and mucinoids on peptic digestion, Bradley and Hodges²³ found the action of mucin to be equivalent to reducing the concentration of active enzyme. The inhibition is one of rate only. Their experiments indicated a temporary delay in the digestive removal of fibrin covered by gastric mucin and by okra. This would appear to be of real significance in preventing interruption of the healing process.

22. Fogelson, S. J.: Gastric Mucin Treatment for Peptic Ulcer: Report Based on Questionnaires, *Arch. Int. Med.* **55**:7 (Jan.) 1935.

23. Bradley, H. C., and Hodges, M.: Effect of Mucin and Mucinoids on Peptic Digestion, *J. Lab. & Clin. Med.* **20**:165, 1934.

In the latter part of 1933 Meyer, Seidmon and Necheles²⁴ reported on the treatment of seventeen patients with ulcer with a preparation of powdered okra. Fourteen noted immediate relief, which was all the more striking as no other forms of treatment were employed.

If the work of these authors is substantiated, the patient's choice between the vegetable mucin of okra, so commonly associated with chicken soup, and the mucin secretion of the hog's stomach would not be difficult to anticipate.

Bulmer²⁵ reports the results in 52 unselected cases of peptic ulcer in which the condition was treated by the parenteral injection of histidine, one of the amino-acids. This study was undertaken because Aron and Weiss had shown that the formation of experimental ulcers in dogs could be prevented by injections of histidine and because excellent relief of symptoms was obtained in 17 cases in which peptic ulcer was so treated. So far as possible Bulmer used histidine. His immediate results showed symptomatic cure in 58 per cent of the cases and failure in 23 per cent. In a follow-up study, 3 patients were found to have a relapse. Gastric ulcers seemed more amenable to treatment than duodenal ulcers. Patients with a short history responded better than those with a long history.* The author states that no final conclusions have been drawn but that he believes that the results are better and quicker than those of the more orthodox methods.

During a six year period at the Wurzburg Clinic, Engel²⁶ studied the effects of foreign protein therapy in cases of gastric and duodenal ulcer. He administered a plant albumin intravenously in a selected group of 70 cases in which there had been no response to the ordinary dietary regimen. A few patients had chills, fever and vomiting. Fifty-eight per cent of the patients became symptom-free, 30 per cent were improved and only 12 per cent remained completely unchanged. Engel considers these results very favorable and states that all patients with an uncomplicated ulcer which does not respond properly to diet should have a course of foreign protein therapy before surgical intervention is considered.

Foreign protein therapy in the treatment of peptic ulcer has been popular abroad but has received little attention in the United States. Cunha²⁷ reports his experiences with the use of a proprietary prepa-

24. Meyer, J.; Seidmon, E. E., and Necheles, H.: Treatment of Peptic Ulcer with Powdered Okra, *Illinois M. J.* **64**:339, 1933.

25. Bulmer, E.: Treatment of Peptic Ulcer, with Note on Fifty-Two Cases, *Lancet* **2**:1276, 1934.

26. Engel, A.: Beitrag zur Kenntnis der Erfolge der "Proteinkörpertherapie" bei Magen- und Duodenalulcus, *Arch. f. Verdauungskr.* **56**:256, 1934.

27. Cunha, F.: Experiences with New Mode of Treating Peptic Ulcer, *Am. J. Surg.* **23**:219, 1934.

CHENEY—GASTRO-ENTEROLOGY

ration containing lipoproteins and emetine. Cunha states that the lipoprotein has a tendency to decrease gastric peristalsis, arrest pylorospasm and promote healing of the local lesion. Emetine relaxes smooth muscle and has antibacterial properties. Fifty-one patients were completely examined and carefully followed. In 29 cases treatment had been completed a year previous to the report. Each patient received 1 ampule of the aforementioned solution intravenously every fourth day for ten doses. No reaction appeared. A dietary regimen was followed for four weeks. In all but 2 patients complete relief from pain occurred promptly, and healing of the ulcer was promoted, as noted by roentgen examinations. Reports of 8 cases, with roentgenograms, are included to emphasize the benefits of protein therapy and to prove that the patients could continue their daily routine while under treatment.

Sandweiss and Meyers²⁸ have tried bacterial vaccines as a form of foreign protein therapy in cases of peptic ulcer. They used a mixed respiratory vaccine in 33 cases of intractable ulcer and treated patients in a total of forty-eight attacks. Remission occurred in 70.9 per cent, but in about one half of these symptoms reappeared in less than three months. Only 1 patient was symptom-free thirty-six months later. A second course of treatment was likely to give either relief for only a short period or no relief. The authors believe that the chief value of this form of foreign protein treatment rests in its capacity for initiating remissions and that cure should not be expected.

Glaessner²⁹ has long advocated an original conception of the cause of peptic ulcer on which he has based his "specific therapy." The normal balance between the pepsin of the gastric secretion and the antipepsin of the wall of the stomach is upset, with a definite diminution in antipepsin and the resultant digestion of the gastric mucosa and formation of ulcer. The parenteral injection of pepsin will stimulate the formation of antipepsin in the stomach, restore this balance and promote healing of the lesion.

In treating about 1,000 patients with peptic ulcer of the stomach and duodenum Glaessner injected a sterile neutral solution of pepsin which produces only a slight reaction. A special dietary regimen was included as a part of the therapy. Excellent results were obtained in about 50 per cent of this large series, and another series is cited in which good results were obtained in 90 per cent. It is impossible to evaluate the exact benefits, if any, of this pepsin therapy from the data presented in the report.

28. Sandweiss, D. J., and Meyers, S. G.: Treatment of Peptic Ulcer with Bacterial Vaccines (Foreign Protein), *Am. J. Digest. Dis. & Nutrition* 1:338, 1934.

29. Glaessner, K.: Organotherapie des Ulcus pepticum, *Wien. klin. Wchnschr.* 47:513, 1934.

Einsel, Adams and Myers ³⁰ have contributed a report on aluminum hydroxide in the treatment of peptic ulcer. In colloidal form it reduces the emptying time of the stomach, lowers gastric acidity and is devoid of deleterious side-effects. With its power of fixing large quantities of hydrochloric acid, it has the advantages of treatment with alkali without the disadvantages of absorbable alkali, and there is no subsequent stimulation to the production of free acid, as with the use of bicarbonate of soda. Several charts are presented illustrating the lowering of gastric acidity by the regular administration of gelatinous aluminum hydroxide. It is pointed out that acidity again increases when alkali therapy is discontinued.

Jones ³¹ discusses the use of insulin in the treatment of peptic ulcer. The rationale of this form of therapy is apparently largely based on the author's familiarity with pertinent investigations in some of the Russian clinics. He states that insulin increases the secretion of the stomach, which assumes an inert type, and that insulin has the properties of a powerful alkalizer. There is a lowering of vagotonus, thus removing the manifestations of spasmophilia. Jones treated 26 ambulatory patients, injecting, on the average, from 20 to 30 units of insulin daily. They were allowed their customary food and were required to take 100 Gm. of mashed potatoes at each of two main meals. Of the 12 patients with "fresh" peptic ulcer, all but 1 were symptom-free within ten days. All gained weight. After from ten to fifteen days, roentgen examination revealed no definite signs of ulcer. Equally good results were attained in 6 cases of recurrent ulcer. Satisfactory improvement with partial relief from pain and gain in weight and well-being occurred in the 8 cases complicated by perigastritis and adhesions. In some cases the ulcer had been recalcitrant to other forms of treatment. The author noted a change from the vagotonic type of stomach to normotonus and also an increase in gastric secretion with a corresponding improvement in appetite; at the same time there was a decrease in gastric acidity.

All the cases of ulcer which have been studied at the Peter Bent Brigham Hospital during the nineteen years of its existence have been studied as regards the results of treatment, which has been some type of Sippy regimen or some form of surgical procedure. Of a total of 1,435 cases, Emery ³² has analyzed 1,253. Nearly all of these have been followed over one year, and 333 were followed for six years or longer.

30. Einsel, I. H.; Adams, W. L., and Myers, V. C.: Aluminum Hydroxide Treatment of Peptic Ulcer, *Am. J. Digest. Dis. & Nutrition* 1:513, 1934.

31. Jones, C. R.: Insulin in the Treatment of Peptic Ulcer, *Am. J. Digest. Dis. & Nutrition* 1:135, 1934.

32. Emery, E. S.: The Treatment of Peptic Ulcer Based on One Thousand, Four Hundred and Thirty-Five Cases, *Am. J. Digest. Dis. & Nutrition* 1:520, 1934.

A striking feature is the small number of cases in which there was complete relief of symptoms. Only 13.7 per cent of the patients receiving medical treatment and 19 per cent of the patients receiving surgical treatment were relieved, while 23.8 per cent of the patients who received no treatment were symptom-free after leaving the hospital. On the other hand, almost half the untreated patients remained unimproved. A table shows the percentage of "satisfactory results" for all types of treatment. A study of this table reveals the fact that medical treatment resulted in a higher percentage of satisfactory results than the surgical methods and that the complete Sippy regimen was 90 per cent satisfactory. Too much attention is paid to the healing of the ulcer and not enough to preventing a relapse after healing has taken place. Emery found the causes of relapses, in the order of their greatest frequency, to be fatigue, emotional disturbances and recurrence of infection. In only 37 cases were dietary indiscretions mentioned as a cause of relapse.

The results of surgery and of medicine in uncomplicated cases are similar. Obstruction was better relieved by surgical intervention. Neither form of therapy was superior to the other in the prevention of bleeding, although surgical procedure will prevent further hemorrhage in a number of cases in which bleeding persists. The height of gastric acidity does not influence the outcome of treatment, but nearly all patients with high acidity who fail to improve have hypersecretion. In these patients jejunal ulcers invariably develop after surgical intervention.

Emery's analysis of the results of treatment in cases of peptic ulcer is not unlike many others which appear every year. It has been included primarily for a basis of comparison with the preceding forms of medical treatment, as it well represents the efficacy of the types of therapy which have thus far survived the test of time.

There is an increasing appreciation of the fact that many patients with ulcer must have continuous treatment, like patients with diabetes or pernicious anemia, and that individualization is necessary in the supervision of each case.

Rachet³³ has made an extensive medical survey of ulcer following gastro-enterostomy. He has considered the immediate and late post-operative treatment and the intestinal disturbances which may develop after such an operation. He concludes that the complications encountered after gastro-enterostomy may be due to the evolution of an ulcer which has persisted despite the operation or may be due to the gastro-enterostomy itself, in that a new gastro-intestinal physiology has been created to which the organism is not adapted. To prevent accidents

33. Rachet, J.: La surveillance médicale des ulcéreux après la gastro-entérostomie, *Bull. gén. de thérap.* **185**:132, 1934.

and to ameliorate the complications is the rôle of medicine after surgical intervention. There is no better example of the necessity for cooperation between the internist and the surgeon than the after-care of patients on whom a gastro-enterostomy has been performed.

In an article on the "Conservative Treatment of Ulcer of the Stomach and Duodenum" Judd and Waldron³⁴ present their views on the most satisfactory methods for surgical control of these lesions. A brief and interesting historical background leads up to a steady undertone of conservatism. The illustrations are profuse and instructive. The authors conclude that the results of excision and gastrojejunostomy amply justify this procedure for gastric ulcer. Several methods of treatment of duodenal ulcer are now available, if properly applied. Gastrojejunostomy, removal of the duodenal lesion with or without excision of part of the pyloric musculature and gastroduodenostomy without removal of the lesion may each be appropriate. There seems to be no good reason for radical resection for duodenal ulcer.

Gastric Neoplasms.—Shay and Schloss,³⁵ because of a case of gastric carcinoma of unusual interest, consider the gastric ulcer-cancer problem with great care and thoroughness. After weighing the evidence for and against the theories of several moot questions they conclude: 1. Gastric ulcer is only infrequently a precursor of a malignant gastric process. 2. From the duration and nature of the symptoms of ulceration of the stomach and from the response to therapy, it cannot be positively stated that the lesion is benign or malignant in any given case. 3. Although gastric anacidity is common in cases of cancer of the stomach, free acid or a normal or high acid content is seen in almost as many cases. 4. The incidence of those cases of carcinoma in which adequate free hydrochloric acid is present is entirely too high to be accounted for by the ulcer-cancer group. 5. Anacidity in cases of gastric cancer is best accounted for by preceding or associated chronic gastritis. 6. Given an ulcerating gastric lesion, anacidity is presumptive evidence in favor of carcinoma, but the presence of normal or increased acidity is of little, if any, value in militating against a malignant process. 7. Roentgenograms are of little help in the present problem.

The case of Shay and Schloss is placed on record because a physician with as wide experience in gastro-enterology as A. F. Hurst stated that he had never observed a case of gastric carcinoma in which free hydrochloric acid was present at an early stage and disappeared as the

34. Judd, E. S., and Waldron, G. W.: Conservative Surgical Treatment of Ulcer of the Stomach and Duodenum, *Am. J. Digest. Dis. & Nutrition* **1**:262, 1934.

35. Shay, H., and Schloss, E. M.: Consideration of Gastric Ulcer-Cancer Problem, with Report of Case of Ulcerating Carcinoma in Which Gastric Acidity Changed from Normal to Anacidity While Under Observation, *Ann. Int. Med.* **7**:1218, 1934.

CHENEY—GASTRO-ENTEROLOGY

disease advanced. Such a change in gastric acidity did occur in the authors' patient, and a series of four fractional gastric analyses are recorded which illustrate the diminution and ultimate disappearance of free hydrochloric acid during the progress of a carcinomatous ulcer.

Bishop³⁶ reports an additional case of cancer of the stomach in the literature on the occurrence of this neoplasm in young persons. Gastric carcinoma is very uncommon in the second decade of life. Bishop's patient was a girl aged 16, who had no gastric symptoms. Gastric of Hodgkin's disease based on a biopsy, the correct diagnosis was not made during life. The anatomic diagnosis was carcinoma of the stomach with extensive metastases, including large masses in both ovaries.

In a case reported in a paper entitled "Total Gastrectomy for Cancer with After Examinations of the Absorptive Capacity of the Intestine," Bull and Stang³⁷ noted an increased amount of protein and fat in the stool. The fat content was the more marked, but the patient had been on a diet relatively rich in fats. The esophagus and small intestine appeared normal on roentgen examination. A year after operation the patient was carrying on his regular work and taking a liberal diet. He had no discomfort from food as long as he avoided large meals.

Dahlgren³⁸ reports an additional case of endothelioma of the stomach which differs considerably from the 11 cases already recorded in the literature. Usually this tumor is endogastric, arising within the stomach, and is not large. Metastases may occur, although in the 6 cases in which operation was performed none were found. The tumor described in detail by the author was exogastric, was large, weighing 2 Kg., and was of benign endotheliomatous nature. The final histologic diagnosis was lymphangio-endothelioma.

DUODENUM

In a discussion on duodenitis and its roentgenologic characteristics, Kirklin³⁹ brings this subject up to date and emphasizes certain features at operation. The lesion in duodenitis is to be distinguished from duodenal ulcer by the lack of formation of a crater and lack of induration, although both show hyperemia and stippling of the serosa. It may occur

36. Bishop, E. L.: Cancer of Stomach in Young Patients, *Am. J. Cancer* 20:807, 1934.

37. Bull, P., and Stang, J.: Total Gastrectomy for Cancer with After-Examinations of the Absorptive Capacity of the Intestine, *Acta chir. Scandinav.* 75:319, 1934.

38. Dahlgren, L.: Endothelioma of the Stomach, *Acta chir. Scandinav.* 75:451, 1934.

39. Kirklin, B. R.: Duodenitis and Its Roentgenologic Characteristics, *Am. J. Roentgenol.* 31:581, 1934.

independently or in association with true ulcer. From the point of view of histologic changes, the relation between duodenitis and duodenal ulcer has not been conclusively determined, although it is evident that at times the first precedes the second. It is desirable to distinguish between these lesions, if possible, in order to select appropriate therapeutic measures.

Clinically, a definite differentiation of these two disorders is not possible, although in duodenitis the symptoms are less severe, are more irregular and are less readily relieved by food and alkalis. In considering the roentgenologic aspects, 32 cases in which operation had been performed and the pathologic diagnosis established by microscopic examination of excised tissue were selected for analysis; the coincidence of peptic ulcer could be rigidly excluded. The first characteristic of duodenitis is hyperirritability of the duodenum, typically manifested in intense spasticity and hypermotility. The bulb is small and deformed, and the configuration of the deformity varies rapidly from moment to moment. The bulbar shadow lacks density, and the shadows are hazy. A second characteristic is the coarsely and irregularly reticular mucosal pattern. A third is the absence of a crater, and the fourth is the absence of gastric retention or other evidence of obstruction. A small hypertonic active stomach completes the typical roentgenologic syndrome of duodenitis. In only one fourth of the cases were the roentgen signs so pronounced that a definite diagnosis was obvious. In 20 of the 32 cases a diagnosis of duodenal ulcer was made, probably because of the deformity of the duodenal bulb, which has long been recognized as a reliable sign of duodenal ulcer.

An extensive study of the clinical significance of duodenal diverticula has been made in Morawitz's clinic in Leipzig. Lemmel's observations⁴⁰ are based on 50 cases occurring among 3,324 patients, on whom roentgen studies of the gastro-intestinal tract were made. In a discussion of the frequency of duodenal diverticula, a table of 9 different autopsy reports is presented in which the incidence varies between 0.5 and 16.2 per cent. Lemmel explains this extraordinary variation as being due to a lack of careful examination on the part of some pathologists. A second table shows the incidence as revealed by roentgen examination to lie between 0.4 and 5.2 per cent. The author's own large series shows the presence of diverticula in 1.5 per cent of cases. The technic of examination is again blamed for the lack of uniformity of incidence. A third table presents the incidence of duodenal diverticula in relation to age groups. The increased percentage of cases with advancing years is striking. It rises from 0.5 per cent at from 30 to 49 years to 2.6 per cent at

40. Lemmel, G.: Die klinische Bedeutung der Duodenaldivertikel, *Arch. f. Verdauungskr.* 56:59, 1934.

from 50 to 69 years, reaching a peak of 9.7 per cent at from 70 to 90 years. It may be stated that 10 per cent of the patients over 70 have the lesion. Its incidence is compared to the frequency of gastric and duodenal ulcer and to gastric cancer. It is much more common than peptic ulcer and almost as common as cancer in the advanced age group.

Contrary to a number of observers, Lemmel states that the majority of duodenal diverticula cause symptoms either directly or indirectly. Gastro-intestinal disturbances and signs of inflammation cannot be clinically localized by any definite symptom complex. The indirect symptoms are due to secondary involvement of the pancreas, bile passages and liver. The presence of cirrhosis of the liver was proved in 10 per cent of Lemmel's cases. In cases of clinically recognized chronic pancreatitis, a diverticulum is often the determining cause. It is the commonest cause of disease in the region of the ampulla of Vater next to cancer and gallstones.

A clinical diagnosis of duodenal diverticulum is possible but must be confirmed by roentgen examination. The cause of the lesion is not congenital but an acquired pulsion diverticulum of old persons and may be compared to hernia elsewhere. Therapeutically, if the diverticulum is producing pressure symptoms in the neighborhood, it must be extirpated or the duodenum resected.

Ettinger and Davis⁴¹ emphasized the importance of the refined compression technic devised by Ackerlund and Berg in the roentgen diagnosis of activity and cure of duodenal ulcer. Few reports of this method of examination have appeared in the American journals. It requires time and skill but will demonstrate the actual anatomic change, namely, the ulcer, with the highest possible detail and nearly as the pathologist sees it. Ettinger and Davis were able to demonstrate the niche in 50 per cent of 48 cases of duodenal ulcer, including instances in which there was no deformity of the cap. When deformity of the cap alone is the basis of diagnosis, as is so often the circumstance, no information can be obtained as to the activity of the lesion. Although clinical symptoms usually clear up quickly after therapy is instituted, roentgen examination six weeks later reveals over half the ulcers unchanged in size. Complete healing finally occurs, as may be demonstrated by roentgen study six months later in a control examination. While certain technical factors may be disturbing in visualization of the niche, the authors think another factor must be considered, namely, gastritis, which practically always accompanies ulcer.

By using the compression technic the roentgenologist can demonstrate the niche in a large percentage of cases of duodenal ulcer and

41. Ettinger, A., and Davis, W. E.: X-Ray Diagnosis of Activity and Cure of Duodenal Ulcer, *Am. J. Digest. Dis. & Nutrition* 1:579, 1934.

thereby play a valuable part in determining the degree of activity. Some excellent illustrative figures accompany this article which are well worth seeing.

Carcinoma of the duodenum is rare. Two cases have been added to the literature by Lisa, Levine and Fitzhugh.⁴² The reports are concise, and illustrations of the pathologic specimens are included. In 1 case the location was periampullary, and jaundice appeared. The other was supra-ampullary, and intense vomiting was present, said to be characteristic of cancer at this site.

Another report of a case of primary cancer of the duodenum brings out some valuable facts. When the patient first came under observation he complained of weakness and vague symptoms in the upper part of the abdomen of three months' duration. Examination revealed anemia and blood in the stools. The gastro-intestinal roentgen study was negative but showed an obvious alteration of mucosal pattern corresponding to the site of lesion proved later. The patient was admitted to the hospital a year later, having had jaundice for two weeks. Roentgen study revealed a filling defect in the second portion of the duodenum, with indications of rigidity of the wall of the intestine in this same area. A cholecystostomy was performed, but the patient died three days later. Necropsy showed the growth to be periampullary, occurring at the commonest site of primary cancer of the duodenum.

Swenson and Levin⁴³ report this case primarily because of the unusual roentgen findings, which might have suggested the correct diagnosis at the first examination. It is difficult to visualize the entire duodenum, and consequently such lesions are all too readily overlooked. This was of particular importance in this case as no metastases were found at autopsy, suggesting that complete excision might have been carried out at the time of the original study and the life of the patient saved.

SMALL INTESTINE

Bickel and Wagner⁴⁴ carried out a long series of observations on intestinal secretion in a woman with a Thiry fistula of the ileum in an endeavor to study the mechanism involved in the production of the secretion and its relation to conditioned and unconditioned reflexes. They compared their findings to those on dogs studied in a similar

42. Lisa, J. R.; Levine, J., and Fitzhugh, W. M.: Primary Carcinoma of Duodenum, *J. Lab. & Clin. Med.* **20**:150, 1934.

43. Swenson, P. C., and Levin, A. G.: Primary Carcinoma of Duodenum: Case Report, *Am. J. Roentgenol.* **31**:204, 1934.

44. Bickel, A., and Wagner, H. I.: Der Mechanismus der Dünndarmsekretion beim Menschen und seine Verknüpfung mit der psycho-physiologischen Sphäre auf dem Wege über "addierte Reflexe," *Arch. f. Verdauungskr.* **55**:53, 1934.

CHENEY—GASTRO-ENTEROLOGY

manner. As the mechanism of intestinal secretion is partly a nervous reflex and partly humorochemical, they considered a mechanical or chemical stimulation of the mucous membrane—which locally excited the intestinal glands to secrete—to represent an unconditioned reflex. Although this seemed to be the only type of reflex in dogs, there is also set up in man a conditioned reflex under the control of the cerebrum, a psychophysiologic process. The existence of such a conditioned reflex is of great significance in the understanding of the secretory neuroses of the intestine.

Alcoholic drinks, amino-acids, a mixed diet and diets rich in protein and in fat produce a more copious secretion from the intestinal glands than carbohydrate nourishment or a fare of green vegetables. The same chemical excitant can produce both a conditioned and an unconditioned reflex, resulting in secretory activity of the intestinal glands. This the authors demonstrated by introducing amino-acid solutions locally through the opening of the fistula into the isolated intestine and in another experiment by mouth. In each experiment active secretion of intestinal juice was noted within a few minutes.

It was found that powdered pancreas strongly stimulates the intestinal glands. Their activity is intermittent, and on the injection of nourishment there is an intermittent period of at least two minutes before intestinal secretion commences. Bickel and Wagner emphasize also that the lack of the unconditioned reflex in dogs may account for many of the discrepancies in trying to apply the results of experiments on intestinal secretion in animals to clinical observations in man.

A critical review of the recent literature on diverticulosis of the small intestine is presented by Chapman.⁴⁵ He was able to discover reports on only 32 typical cases. They are discussed and analyzed. A hitherto unreported case of his own is described. An old man with psychosis had been under observation in the hospital about two months. No noteworthy gastro-intestinal symptoms were observed. He died after a fall. About 3 or 4 feet (91 to 121 cm.) of the jejunum showed a great number of diverticula opening outward at the mesenteric attachment. The size of the evaginations varied from hardly discernible diverticula to some as large as 4 cm. in diameter.

Schmidt and Guttman,⁴⁶ in an article entitled "Multiple Diverticula of the Jejunum and Duodenum Simulating Gastric Diverticula and Complicated by Cholelithiasis," present a most instructive case and discussion

45. Chapman, J.: Report of Case of Diverticulosis of Small Intestine with Critical Review of Recent Literature, *Ann. Int. Med.* **7**:1376, 1934.

46. Schmidt, E. A., and Guttman, P. H.: Multiple Diverticula of Jejunum and Duodenum Simulating Gastric Diverticula and Complicated by Cholelithiasis, *Am. J. Roentgenol.* **31**:200, 1934.

of jejunal diverticula. Their patient had a laparotomy with removal of the appendix and gallbladder six weeks previously elsewhere, but serious gastro-intestinal symptoms persisted. The roentgen diagnosis after an incomplete examination owing to the patient's poor condition was duodenojejunal diverticulosis. As vomiting persisted, another operation was attempted, but the patient died six hours later. Preoperative and postmortem roentgenograms are reproduced illustrating the lesions found.

Fifty-nine diverticula were found in the jejunum and three in the duodenum, mostly between the layers of the mesentery. They appeared to decrease in size distally. In the smallest ones all the layers of the intestine were present, but in the large ones the muscularis externa was absent at the apex of the pouch. As both true and false diverticula were thus represented in the same patient, it would be less confusing simply to designate all lesions of this type as pulsion diverticula. Jejunal diverticula are very rare and usually do not cause symptoms, as in this case, as death was due to postoperative paralytic ileus and obstructive jaundice caused by a gallstone in the common duct. Diverticula are most frequently found accidentally on postmortem examination. Occasionally, after roentgen study, the lesions are thought to be gastric, owing to overlapping diverticular shadows of the small intestine. This difficulty has been noted previously with duodenal diverticula alone.

Three years ago Crohn, Ginsburg and Oppenheimer described a new disease of the small intestine, which they termed "regional ileitis." Since they called attention to this condition a number of reports on the subject have appeared, greatly amplifying the knowledge and broadening the conception of the disorder. Three articles were published in the *American Journal of Digestive Diseases and Nutrition* during 1934, which give an excellent picture of a new clinical syndrome.

Under the title "The Broadening Conception of Regional Ileitis," Crohn⁴⁷ reports 3 cases to illustrate that involvement of the intestine is much more widespread than the original designation of the disorder implies. The first patient had eight laparotomies between 1917 and 1934, without the exact cause of the trouble being ascertained. Appendectomy, intestinal resection and repair of fecal fistulas had been performed. Under Crohn's direction a ninth operation was carried out with resection of 152 cm. of small and large intestine, and the patient made an uneventful recovery. According to the pathologic report on the specimen removed there were "annular ulcerations with nonspecific, chronic inflammation of the ileum; no tuberculosis in the specimen submitted."

47. Crohn, B. B.: Broadening Conception of Regional Ileitis, *Am. J. Digest. Dis. & Nutrition* 1:97, 1934.

CHENEY—GASTRO-ENTEROLOGY

It is emphasized that in three years the author has seen between 30 and 40 cases of the condition under discussion and that it is not rare. Surgeons should be cognizant of this fact. Symptoms suggesting appendicitis warrant close scrutiny of the coils of the lower portion of the ileum at operation. External fistulas of the abdominal wall ultimately occur and also spontaneous intestinal fistulas, which tend to heal after excision of the ileum. Peculiarly enough, fistulas of the ileum do not include the bladder.

In Crohn's second case of ileitis the condition was diagnosed roentgenographically. The patient complained of a constant mild diarrhea for two years. The first impression was of nontropical sprue, as there were hyperchromic anemia and hypoproteinemia with edema. Roentgen examination of the gastro-intestinal tract revealed the lower portion of the ileum to be irregular, and rounded shadows suggesting ulceration or small polyps were scattered widely in the ileum and in the lower portion of the jejunum. At operation 60 cm. of thickened and inflamed ileum was resected. The patient died ten days later. On the lower portion of the resected specimen diffuse ulcerating inflammation was observed. Higher up the lesion became alternating and scattered, involving the lowest portion of the jejunum as well. This case is interesting clinically because it is an instance of ileitis devoid of pain and pathologically because it is the first encountered by Crohn in which the "regional ileitis" had involved the lowermost portion of the jejunum.

In the third case Crohn termed the condition familial ileitis, as he had seen a boy of 14 with the condition, and subsequently the sister of this boy, 32 years old, was operated on for the same condition. The pathologic specimens obtained in both instances were characteristic of regional ileitis. The occurrence of these 2 cases in one family may be purely accidental, may have significance as to a congenital predisposition or may be due to a transmissible causative agent in this disease.

Under the name chronic ulcerative enteritis, Corr and Boeck⁴⁸ report an additional case belonging to the group of regional ileitis. The authors believe that this original term is not sufficiently comprehensive and that chronic cicatrizing enteritis is not exact, as it applies only to a late stage of the disease. The basic pathologic process is ulceration, and the chronicity produces a picture not unlike chronic ulcerative colitis.

The case was remarkable in that during the six years of the course all four of the different clinical phases mentioned in the literature were presented. Intestinal symptoms and cramps during the first year led to appendectomy, at which time the intestine was said to have been

48. Corr, P., and Boeck, W. C.: Chronic Ulcerative Enteritis, *Am. J. Digest. Dis. & Nutrition* 1:161, 1934.

“reddened and diseased.” The second phase of chronic ulcerative enteritis was represented by the same symptoms, with alternating diarrhea and mild constipation, recurring periodically during the next four years. The patient became an invalid. She had received much anti-amebic therapy, as it was reported that amebas had previously been found in the stools. Attacks of severe abdominal pain with vomiting and an increase in the diarrhea suggested the development of the later phase of stenosis with obstructive symptoms. An operation for suspected intestinal obstruction was performed. Rectovaginal and abdominal fistulas formed, representing the fourth phase of the disease. The patient died of inanition. Pathologically, the striking features were that the terminal portion of the ileum was free from lesions; all but about 3 feet (91 cm.) of the small intestine was involved; the presence of pseudopolyposis surrounded by ulcerating areas was similar to that reported in cases of chronic ulcerative colitis, and the discovery of active inflammation indicated continued activity of the disease. A possible relationship of amebiasis to the underlying cause of the disease is mentioned.

This same type of disorder is intensively studied by Brown, Borgen and Weber ⁴⁹ in a report entitled “Chronic Inflammatory Lesions of the Small Intestine (Regional Enteritis).” The authors are impressed by the fact that inflammatory ulcerative disease in the jejuno-ileocecal coil or regional areas of the colon pathologically is indistinguishable from that in the terminal portion of the ileum and that the involvement appears to be a clinical and not a pathologic entity. Their detailed report of the clinical and pathologic features comprises a study of 18 patients recently observed.

The disorder may occur at almost any age and is twice as common in the male as in the female sex. In half the cases the ileum alone was involved. At operation the lesions were remarkably similar. An inflammatory process involving all the layers of the intestine and rather sharply localized in area, associated with hypertrophy suggesting a stiff rubber tube, were universally noted. Most of the patients had been ill for years, and 10 had undergone previous operations, mostly for appendicitis. An abnormal condition of the ileum or colon had been noted in 6 patients, thought to be tuberculosis, Hodgkin’s disease or intestinal inflammation of unknown etiology.

The most predominant complaint was pain, for which none of the patients could find any constant relief. Diarrhea was the chief complaint in only a third of the cases, but in general the stools were loose

49. Brown, P. W.; Borgen, J. A., and Weber, H. M.: Chronic Inflammatory Lesions of Small Intestine (Regional Enteritis), *Am. J. Digest. Dis. & Nutrition* 1:426, 1934.

and watery, with much urgency and cramping and without visible blood. Vomiting was marked in 9 cases. The situation and character of the lesion seemed to be a factor in this symptom. Recurrent fever appeared in 10 cases, but no rise in temperature was ever noted in the other 8. Loss of weight was the striking feature in a majority of the cases. The authors were impressed by the paucity of physical findings. Emaciation and moderate anemia were usually the only objective signs. No definite leukocytosis occurred.

From a roentgenologic point of view, it is important to visualize the results of the pathologic changes which produce mural thickening with consequent narrowing of the intestinal lumen, stiffening and shortening of the involved portion and destruction of mucosa. These changes are readily revealed but demand close scrutiny of each segment by multiple roentgenoscopic observations of the descending opaque meal and careful investigation of the terminal portion of the ileum after it has been distended by reflux of the opaque enema through the ileocecal valve. Interpretation of the findings requires extreme caution. The differential diagnosis of regional ileitis involves chiefly appendicitis in the early stage and intestinal tuberculosis in all stages. The presence of tuberculosis could not be established in any of the cases despite a careful search in each. "Inflammatory lesion of the bowel" was the preoperative diagnosis in 8 of the 18 cases.

Treatment essentially is surgical. Entero-anastomosis proved sufficient to relieve some patients, but resection of the diseased segment is usually necessary. The end-results of operation are often remarkably good and in some instances may be designated as a complete cure.

LARGE INTESTINE

Scholz⁵⁰ has made an exhaustive and illuminative study of the problem of chronic appendicitis. After a relatively brief survey of the general subject, the author observes that the problem may best be solved by the investigation of three questions of prime importance: 1. Is local tenderness, as ascertained roentgenoscopically, the only reliable sign of appendicitis? And what is the diagnostic status of the other so-called signs? 2. What rôle may roentgenology play in differential diagnosis, and to what extent may it reliably serve as a means for preventing unnecessary operations? 3. Are anatomic findings or therapeutic results the best criteria for the correctness of the diagnosis of chronic appendicitis?

Several interesting series of cases of appendicitis are compared, correlating the clinical, roentgen and anatomic findings. The findings in

50. Scholz, T.: The Solution of the Roentgen Diagnostic Problem in Chronic Appendicitis, *Am. J. Roentgenol.* **31**:792, 1934.

these series are also compared to the findings in cases of other abdominal conditions and also to findings in a series of normal persons. The conclusions seem warranted. Scholz states that roentgenology is the best diagnostic method in chronic appendicitis, and that its main value lies in the differential diagnosis from other important lesions which may simulate it. The roentgen examination must be made by a competent roentgenologist. The roentgen diagnosis is based on a single sign, namely, local tenderness as elicited by palpation over the visualized region of the appendix. All other so-called roentgen signs are of no diagnostic value. Chronic gross anatomic changes occur in an appreciable number of clinically normal persons, and microscopic anatomic changes are found in practically every adult appendix. Anatomic changes, therefore, cannot be taken as a reliable criterion for the correctness of the diagnosis of chronic appendicitis. A much better criterion is the therapeutic result.

The recent outbreak of amebiasis in Chicago has stimulated medical thought on the general subject of intestinal ulceration. Felsen⁵¹ gives a complete description of ulcerative disease of the intestine under the title "Practical Etiological and Clinical Consideration of Intestinal Ulceration with Especial Reference to Amoebic Dysentery, Bacillary Dysentery and Idiopathic Ulcerative Colitis." The virtue of this report lies largely in the fact that it correlates the general knowledge of a variety of conditions which are usually considered independently and that it simplifies the practical problem which confronts the average physician as to how to differentiate the various types of intestinal ulceration. A few points are worthy of review.

As pathogenic bacteria can pass through healthy intestinal mucosa, ulceration of the intestine cannot be due solely to local invasion by living bacteria. In bacillary dysentery the lesions are probably due to the excretion of toxins through the intestinal wall and they may be compared to the lesions in mercury and arsenic poisoning. On the other hand, ulceration due to direct local action on the intestinal wall is best exemplified by infection due to *Endamoeba histolytica*. Ulcers may also be "trophic" or embolic, and in cases of neoplasms they are essentially due to central necrosis. Their location in the intestine will have considerable bearing on the types of symptoms produced. Felsen has included some diagrams on the distribution and character of lesions in cases of ulcerative disease of the large intestine and terminal portion of the ileum which are highly instructive.

51. Felsen, J.: Practical Etiological, Pathological and Clinical Consideration of Intestinal Ulceration, with Especial Reference to Amebic Dysentery, Bacillary Dysentery and "Idiopathic" Ulcerative Colitis, *Am. J. Digest. Dis. & Nutrition* 1:297, 1934.

The general symptoms of bleeding, mucus and pus in the stool, tenesmus, abdominal pain and diarrhea are presented largely on a physiologic basis. The salient features of the major diseases causing intestinal ulceration are presented, but nothing particularly new is included.

Bargen,⁵² in an article entitled "Chronic Ulcerative Colitis: Trends in Its Present Day Management," discusses the forms of therapy available and their relative value, on the basis of eleven years' experience with 1,472 cases. Rest is extremely important, just as in other chronic conditions, such as tuberculosis. Immunization by serums or vaccines is strongly advocated, and repeated courses of injections should be carried out. Such a procedure has proved the greatest single item in preventing recurrence of the disease. Transfusions of blood are of great value in selected cases. The diet should not be too greatly restricted. Adequate amounts of foods digested almost entirely in the small intestine should be given. A table of a desirable dietary regimen is presented. No drugs are specific, but a few are of value in symptomatic therapy. All foci of infection must be removed. Intestinal irrigations not only are not helpful but may actually be harmful. Surgical procedure, such as ileostomy, should be avoided, as the risk of the operation is great and the end-results disappointing.

Carcinoma is the commonest tumor of the large intestine. Sarcoma occurs less frequently. These two forms of malignant process and adenomatous polyps represent the majority of new growths of this region. However, a number of other tumors, usually benign, may occur and produce constitutional symptoms or obstructive phenomena. As the clinical picture they produce is usually thought to be due to carcinoma, a patient may be denied adequate treatment on the erroneous assumption that the condition is malignant and nothing beneficial can be accomplished.

As these uncommon tumors of the large intestine may have to be considered in the differential diagnosis of any given case, Bargen and Dixon⁵³ briefly describe them and their incidence. Fibroma is extremely rare. Eight cases have been observed at the Mayo Clinic, and the history of 1 case is reported. Tumors of pure muscle are exceedingly rare. These myomas have a tendency to recur after excision and to become malignant. Adenomyoma of the sigmoid colon usually develops in relatively young women secondary to pelvic disease but has appeared in men. Angioma is the rarest type of tumor found in the large intestine

52. Bargen, J. A.: Chronic Ulcerative Colitis: Trends in Its Present-Day Management, *Am. J. Digest. Dis. & Nutrition* 1:190, 1934.

53. Bargen, J. A., and Dixon, C. F.: The Uncommon Tumors of the Large Intestine, *Am. J. Digest. Dis. & Nutrition* 1:400, 1934.

and is probably congenital. Lipoma, except for adenoma, is the most frequently encountered benign tumor of the gastro-intestinal tract. It develops in older patients and may produce obstruction. The clinical differentiation from cancer is difficult. Cholesteatoma, dermoids and teratoma have all been reported. In a few cases, cysts of the cecum have been described. Endothelioma may arise in the rectum proper, but through early invasion of the spinal cord the symptoms are predominantly neurologic.

The treatment of all these lesions is surgical, and highly satisfactory results are frequently obtained.

The outbreak of amebiasis in Chicago in the summer of 1933 and the consequent dissemination of infected persons to all parts of the United States stimulated a hitherto unapproached interest in this parasitic infection in this country. The medical literature of the next year clearly shows how unfamiliar the majority of physicians were with the clinical manifestations and methods of diagnosis of a disease which is of daily occurrence in the tropics and is well known to physicians practicing there. Most of the papers consist of reviews of already established facts and reports of cases appearing locally and add little to the basic knowledge of infection by *E. histolytica*. Such a reemphasis of this subject is desirable; so a few reports of amebiasis are abstracted.

"Amebiasis and Amebic Dysentery" is the title of an excellent article by Craig,⁵⁴ who is a recognized authority in this field of medicine. It is a general review, emphasizing many points applicable to the problems raised by the presence of this parasitic infection in most cities. Craig states that unfortunately the term amebic dysentery has become synonymous with amebiasis. It should be clearly understood that the term "amebiasis" means the invasion of the tissues of man by *E. histolytica* and the term "amebic dysentery" means a symptom complex characterized by a bloody mucoid diarrhea which may occur as one of the clinical manifestations of amebiasis. The first is common in the United States; the second is rare and is not a disease entity but a part of the picture of amebiasis.

Although the geographic distribution is world-wide, wherever sanitation and personal hygiene are poor, amebiasis is prevalent, whether in the tropics or in the temperate zone. The vast majority of people in this country infected with *E. histolytica* do not have dysentery. The incidence of infection in the United States may be conservatively estimated as between 5 and 10 per cent of the population. This makes amebiasis a most serious public health problem, particularly as all untreated or improperly treated persons with amebic diarrhea become

54. Craig, C. F.: Amebiasis and Amebic Dysentery, *Am. J. Digest. Dis. & Nutrition* 1:4, 1934.

carriers of the cysts of the parasite, making them potential sources of infection to others. The disease is spread through a contaminated water supply, by the use of human excretion in the fertilization of vegetable gardens, by the contamination of food and drink by the droppings of flies and by the contamination of food and drink by handlers of food who are carriers of the ameba. Strains of *E. histolytica* apparently do not differ in virulence, but the infection is more likely to assume a severe form under conditions greatly depressing natural human resistance, such as those which existed in the early days of the Philippine insurrection.

The pathologic process of amebiasis is well recognized. It is noteworthy that marked amebic ulceration may exist in the intestine of man without producing symptoms of severe diarrhea or dysentery. The symptomatology of the disease is most likely to be represented by a host of gastro-intestinal complaints and disturbances of the nervous system rather than by the spectacular symptoms of "amebic dysentery." The exact incubation period of the dysentery is unknown but averaged sixty-four and eight-tenths days in 4 volunteers experimentally infected. The impression that fever never occurs is incorrect, as the temperature may vary between 100 and 102 F. in the severe cases. Fulminating types of amebic dysentery are rare. In addition to the usual physical signs in the abdomen, tenderness and pain in the hepatic area always indicate the presence of hepatitis and possible commencing formation of an abscess in the liver. Slight anemia and leukocytosis are present, but Craig states that eosinophilia has not occurred in his experience.

Physicians are much handicapped in making the diagnosis of amebiasis and amebic dysentery, because at present comparatively few laboratory technicians and physicians are capable of differentiating the five different species of ameba living in the human intestine. An accurate diagnosis demands the demonstration of *E. histolytica* in the feces of the patient. A simple microscopic preparation of an unstained specimen of the stool is successful in demonstrating the parasite in the vast majority of cases of acute amebic dysentery. Identification of the cysts may require stained preparations, or culture methods may be employed in doubtful cases. The complement-fixation test cannot be used alone in diagnosis but is highly accurate.

A most important prophylactic measure is the routine examination of handlers of food and their proper treatment, but facilities permit this to be done on only a small scale at present. Treatment as a rule is highly satisfactory. Carbarsone, formyl meta-amino-para-hydroxy-phenyl arsinic acid, or vioform will clear up all but the most chronic infections. Craig emphasizes that emetine should never be used for the treatment of carriers but is most valuable in the control of dysenteric symptoms.

Brown⁵⁵ has presented the history of 5 cases illustrating certain atypical types of amebiasis. The first patient was hospitalized for bronchopneumonia, and on the tenth night began to pass bright red blood in the stool. Despite repeated transfusions he died. At necropsy ulcerated areas were noted in the cecum and rectum. Smears from the ulcers showed *E. histolytica*. Such a massive hemorrhage from the large intestine is rare in amebiasis. The second patient presented symptoms and signs of subacute appendicitis. At operation the appendix seemed normal, but the colon was involved in a diffuse inflammatory process. A subsequent examination of the stool revealed *E. histolytica*. In the third case there was a palpable mass in the right lower quadrant, and proctoscopic examination revealed large ulcerated areas throughout the rectum and sigmoid. An opaque enema revealed a filling defect involving the cecum. Two examinations of the stool failed to disclose any parasites. Antiamoebic therapy was instigated; the cecal mass disappeared, and the ulcers cleared up. Tumefactive masses caused by *E. histolytica* are not common and may well be confused with carcinoma.

The fourth patient had complained of bloody diarrhea for two years, and weakness and anemia were marked. Examinations of the stool gave negative results. Proctoscopic and roentgen signs of chronic ulcerative colitis were present. Many forms of therapy had been unavailing. On the first examination of the stool the specimen was almost alive with *E. histolytica*. All the symptoms cleared up rapidly with antiamoebic therapy. This case of ulcerative colitis proved to be definitely parasitic in origin. The fifth patient had a pelvic abscess, and the condition improved with antiamoebic therapy. A parasitic origin of the abscess was not proved, but it was assumed that an amebic ulcer had ruptured into the pelvis.

55. Brown, P. W.: Certain Atypical Types of Amebiasis, *Am. J. Digest. Dis. & Nutrition* 1:10, 1934.

Book Reviews

Chirurgie du pancréas. By P. Brocq and S. Miginiac. Price, 75 francs. Pp. 427, with 74 illustrations. Paris: Masson & Cie, 1934.

The authors have completed an excellent monographic exposition of the injuries to, and surgical diseases of, the pancreas. The book is written in an admirable style with no tinge of lucubration, and the various surgical disorders of the pancreas are treated systematically in the accepted textbook fashion. The abundant but compendious observations on the histories of cases appropriately demonstrating the diverse clinical manifestation of each disease deserve unmitigated approbation. Although the illustrations in themselves are surprisingly deficient in artistic excellence, nevertheless they are adequately elucidative and sufficiently representative. Showing a keen sense of proportion, the authors have devoted over half the volume to the more common acute and chronic inflammatory diseases and allocated the remainder to traumas, cysts, syphilis, tuberculosis, lithiasis, fistulas, malignant tumors, and anomalies of the pancreas.

In the discussion of pancreatic injury the authors call attention to its apparent rarity in observation and to the actual infrequency in diagnosis. They opine that the explanation lies in the fact that: (1) injury to an organ so deeply situated is nearly always accompanied with associated lesions of such severity as to result in a fatal termination before time for surgical intervention; (2) because of technical difficulties, the examination of the pancreas during an emergency laparotomy may not be sufficiently thorough to reveal a wound of the pancreas. They make the bold statement that the preoperative diagnosis of a wound of the pancreas has never been made. This is more readily comprehended after one reads their chapters dealing with diagnosis.

As a matter of fact, the diagnosis of surgical diseases of the pancreas in general is woefully unsatisfactory. Although in recent years rapid progressive strides have been made toward a better understanding of the pathologic alterations of the physiology of this vital organ, the clinical manifestations are not sufficiently well defined and the laboratory and roentgen technics are not adequately developed to be of commensurate diagnostic value.

Apropos of the pathogenesis of acute pancreatitis, the authors succinctly but thoroughly discuss the vascular and the better accepted canalicular theories. They are of the opinion that this condition rarely, if ever, occurs in a normal gland. Although acute pancreatitis can be produced experimentally in normal glands of animals by the injection of various substances into the canal and by ligation of vessels, these are intensive methods. However, in an abnormal gland or one chronically diseased these exciting factors need not be so intensive. They believe that undoubtedly there are multifarious causes and discuss the possibility of a primary vascular injury, the rôle of infection, the more recently introduced allergic theory and the older theory of occasional activation of the ferments of the pancreatic secretion.

Particular emphasis is laid on the necessity of differentiating true from false cysts in order to institute rational surgical measures. As the latter have no true wall, it is useless and dangerous to attempt extirpation, which is the method of choice for the former, in which there is a true wall and in which a line of cleavage can be found. Marsupialization or incision and drainage suffice in the treatment of false cysts.

A brief discussion of aberrant pancreas and annular pancreas comprises the closing chapter on anomalies. The former is of particular interest to the surgeon, aside from its rarity, because of its confusion clinically and pathologically with peptic ulcer. It usually occurs as a reddish-yellow or brown, indurated plaque in the neighborhood of the pylorus on the stomach or duodenum and may be easily mistaken for an ulcer. The treatment is simple excision.

Although slight partiality is manifested in the citations and the appended bibliography is arranged in a rather slipshod fashion, nevertheless the latter is up to

date. The book is heartily recommended to those having an easy knowledge of French, because to be of value it requires a thorough study.

Grundzüge der pathologischen Physiologie. By Hans Lucke. Price, 6.60 marks. Pp. 195. Berlin: Julius Springer, 1934.

This book is published, as the title implies, to bring out the principal facts of pathologic physiology in a brief, concise fashion. Lucke has kept the needs of the student primarily in mind in providing a short survey of the field of pathologic physiology in a form which omits most of the confusing details and controversial aspects. The book thus supplies an opportunity for the unfamiliar reader to grasp a general understanding of the field in a short time, so that he may be oriented when breaking into the more detailed works and literature. No pretense is made at treating the subject exhaustively.

Lucke considers his subject in the usual systematic way under the major headings of metabolism of foodstuffs, total metabolism, mineral and water metabolism, vitamins and hormones and then considers the various systems, as the hematopoietic, respiratory, circulatory, renal, gastro-enteric and nervous, as well as the regulation of the body temperature and the problems of infection, immunity and allergy. Under these headings the groundwork for further more elaborate consideration is laid down in typical, terse, German style. Because of the book's purpose, no doubt, some of the newer advances in the mechanisms of disease, especially those of controversial nature, are entirely omitted or given a position of reduced importance and little emphasis. This is true of the recent work on the relationship of the anterior pituitary gland to sugar metabolism, of hyperparathyroidism and especially of the cortical extracts of the adrenal gland and sodium chloride metabolism in Addison's disease. Fat metabolism is little more than mentioned, a fact which does not reflect on the author's neglect but indicates that present knowledge of the mechanisms and pathologic physiology of fat metabolism is very meager. There are no illustrations or diagrams, nor is there a bibliography.

The reviewer recommends the book heartily for the purpose indicated. It is, of course, of limited value as a source book and reference manual.

Diseases of the Chest. By J. Arthur Myers. Edited by Morris Fishbein. Price, \$3. Pp. 385, with 62 illustrations. New York: National Medical Book Company, Inc., 1935.

This book from the pen of a recognized authority on tuberculosis and diseases of the chest fulfils very well the hopes of the reviewer. Particularly instructive are the chapters on tuberculosis, of which the author has been a close student for many years. Much of the material in this book is not readily available in general texts, and it should prove a useful guide to the practitioner who is interested in diseases of the chest.

News and Comment

CENTRAL SOCIETY FOR CLINICAL RESEARCH

The Eighth Annual Meeting of the Central Society for Clinical Research will be held at the Drake Hotel in Chicago on Friday and Saturday, November 1 and 2. The meetings are open to all who are interested in clinical medicine.

CYCLIC RESPONSE OF THE THYROID GLAND TO EXPERIMENTAL EXCITATION AND DEPRESSION

HARRY B. FRIEDGOOD, M.D.*

BOSTON

The effect of iodine on the hyperthyroidism of exophthalmic goiter is dramatic not merely because of its striking depressant activity on the clinical manifestations of the disease but also on account of the temporary duration of its beneficial influence. Although the details of this unique behavior of iodine have been studied extensively,¹ little attention has been directed to their specific physiologic significance.

It is proposed, therefore, to present the results obtained from published and unpublished experiments on the functional activation and depression of the thyroid gland of the guinea-pig, to correlate these findings with relevant clinical and experimental data from the literature and finally to interpret them in terms of a relatively simple conception.

Such a study of the thyroid gland under diverse experimental and clinical conditions has revealed that its behavior is consistently influenced by a factor which limits its ability to respond indefinitely to any stimulus tending to disturb its functional stability.

The recognition and appreciation of this general principle by which the functional activity of the thyroid gland appears to be regulated

* Jacques Loeb Fellow in Medicine.

Presented before the Boston Society of Biologists, Oct. 24, 1934.

From the Department of Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine.

This work was aided in part by a grant from the Committee on Scientific Research of the American Medical Association.

1. (a) Starr, P.; Walcott, H. P.; Segall, H. N., and Means, J. H.: The Effect of Iodin in Exophthalmic Goiter, *Arch. Int. Med.* **34**:355 (Sept.) 1924. (b) Means, J. H., and Richardson, E. P.: The Diagnosis and Treatment of Diseases of the Thyroid, in Christian, H. A.: *Oxford Monographs on Diagnosis and Treatment*, New York, Oxford University Press, 1929, vol. 4. (c) Thompson, W. O., and Thompson, P. K.: Exophthalmic Goiter: The Development of Refractoriness to Iodine, *Arch. Int. Med.* **48**:351 (Sept.) 1931. (d) Means, J. H.; Thompson, W. O., and Thompson, P. K.: On the Nature of the Iodine Reaction in Exophthalmic Goiter with Particular Reference to the Effect of Iodine Late in the Course of the Disease, *Tr. A. Am. Physicians* **43**:146, 1928. (e) Means, J. H., and Lerman, J.: The Action of Iodine in Thyrotoxicosis with Special Reference to Refractoriness, *J. A. M. A.* **104**:969 (March 23) 1935 (Dr. Means furnished me this material in a personal communication).

may yield further insight into the perplexing transitory character of the remission produced by iodine.

METHOD AND MATERIAL

One hundred and sixty-one guinea-pigs were utilized for the observations on which this study is based. Of these, 111 were used in the experiments on metabolism while 50 untreated normal animals were killed after a period of observation of from three to four weeks to control the histologic studies on the experimental animals. Of the 111 animals, 61 received injections of an alkaline extract of the anterior lobe of the hypophysis; 45 received simultaneous injections of the anterior lobe pituitary extract and sodium iodide, and 5 were given sodium iodide under experimental conditions which are indicated in connection with the detailed observations.

Determinations of the basal metabolic rate were carried out in a modified Benedict closed-circuit apparatus at 32 C., which is the critical temperature of the guinea-pig. Under these conditions there was a maximum variation in the normal basal metabolic rate among all the animals of approximately 10 per cent, while successive daily determinations on the same guinea-pig usually checked to within 5 to 8 per cent.

An increase in basal metabolic rate of more than 10 per cent was regarded as a significant change under the current experimental conditions.

EXCITATION OF THE FUNCTIONAL ACTIVITY OF THE THYROID GLAND

Relation Between the Thyroid Gland and the Anterior Lobe of the Hypophysis.—It is well established that the functional state of the thyroid gland can be greatly influenced by the anterior lobe of the hypophysis. Ablation of the anterior lobe of the pituitary gland causes a retardation of development or atrophy of the thyroid gland, as a result of which there is a significant decrease of the basal metabolic rate, while appropriate replacement therapy obviates this evidence of functional deterioration.²

It is also well recognized that injections of an acid or alkaline extract of the anterior lobe of the hypophysis stimulate the functional activity of the normal thyroid gland by virtue of a thyreotropic substance. Such extracts initiate metamorphosis in the larvae of axolotls, frogs and salamanders because of this induced hyperthyroidism, a state which can be measured quantitatively and detected histologically.²

Injections of potent extracts of the anterior lobe of the hypophysis also induce similar functional and histologic changes in the thyroid gland of birds and mammals.² In guinea-pigs they cause obvious hyperthyroidism which closely resembles exophthalmic goiter in man³ and which is characterized by the following: (1) a cycle of histologic changes

2. A fairly extensive and detailed bibliography which is appended to the paper by Friedgood³ should be consulted.

3. Friedgood, H. B.: Experimental Exophthalmos and Hyperthyroidism in Guinea Pigs; Clinical Course and Pathology, Bull. Johns Hopkins Hosp. 54:48, 1934; J. A. M. A. 100:1521 (May 13) 1933.

in the thyroid gland;⁴ (2) a decrease in the total iodine and protein-bound iodine in the thyroid gland, simultaneously with an increase of these substances in the circulating blood stream;² (3) a transitory increase in the basal metabolic rate and in the basal pulse rate;⁴ (4) a rapid loss of weight;⁴ (5) exophthalmos,⁴ and (6) undue nervous excitability.⁴

The behavior of this experimental syndrome in animals is likewise similar to that of the clinical course of exophthalmic goiter in man and is principally characterized by the occurrence of cycles in the symptomatic intensity of the malady,³ in addition to a remarkable susceptibility to the influence of iodine,⁵ albeit apparently a temporary one.⁶

Effect of Anterior Lobe Pituitary Extract on the Thyroid Gland of Guinea-Pigs.—Daily intraperitoneal injections of an alkaline extract of the anterior lobe of the hypophysis were given to the 61 guinea-pigs in this series in doses of 2 cc. per kilogram of body weight. The extent and duration of the response to the thyreotropic influence exerted by the extract were marked by wide individual variations. The majority of the animals reacted to this stimulus by a metabolic disturbance which revealed well defined periodic variations in intensity, a circumstance which deserves emphasis in view of the relatively brief period during which the extract is capable of exerting an influence on the functional behavior of the thyroid gland.

The initial departure from the normal metabolic level is characterized by a prompt increase in the rate of consumption of oxygen, starting within eighteen hours and reaching a maximum elevation varying from +22 per cent to +66 per cent about the seventh or eighth day of the experimental period.⁷

The rise in the basal metabolic rate, the development of the hypertrophic and hyperplastic changes in the thyroid gland, the increase in the concentration of iodine in the circulating blood and the decrease in the iodine content of the thyroid gland take place coincidentally.⁴

A striking, spontaneous remission develops in spite of, or because of, the continued administration of anterior lobe pituitary extract after the peak of consumption of oxygen has been reached in the second period of the metabolic disturbance. As a result of this phenomenon,

4. Footnotes 2 and 3.

5. (a) Siebert, W. J., and Thurston, E. W.: The Effects of Combinations of KI with Acid Anterior Pituitary Extracts, KI with Armour's Anterior Pituitary, and KI with Thyroid Substance upon Basal Metabolism in Guinea Pigs, *J. Pharmacol. & Exper. Therap.* **46**:293, 1932. (b) Friedgood, H. B.: The Effect of Iodin in Experimental "Exophthalmic Goiter" of the Guinea Pig, *ibid.* **51**:134, 1934.

6. Friedgood, H. B.: The Iodin Remission in Experimental "Exophthalmic Goiter" of Guinea Pigs, *J. Pharmacol. & Exper. Therap.* **53**:46 (Jan.) 1935.

7. Footnotes 3 and 6.

the basal metabolic rate returns to its original value within a period varying from one to three weeks. Sometimes, however, the rate of consumption of oxygen descends below its normal level at the end of this period, and this suggests that prolonged stimulation leads either directly or indirectly to a state of hypofunction of the thyroid gland.³ The latter is contrary to the experience of Siebert and Thurston⁵ and was not recorded by Anderson and Collip⁸ in their initial observations on guinea-pigs.

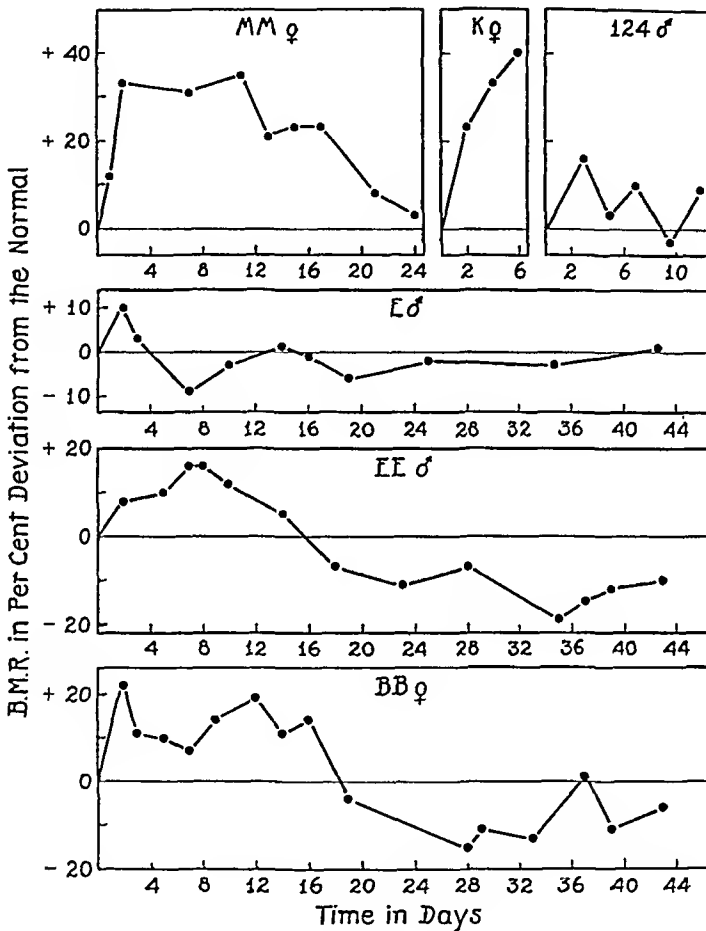


Chart 1.

The beginning of the spontaneous remission apparently takes place when the most marked histopathologic changes have developed in the thyroid gland.³ The spontaneous involution of this parenchymal hypertrophy and hyperplasia and the reaccumulation of acinar colloid lag moderately behind the decreasing basal metabolic rate in this period.³ By the time the basal metabolic rate has reached its normal level, how-

8. Anderson, E. M., and Collip, J. B.: Thyreotropic Hormone of Anterior Pituitary, *Proc. Soc. Exper. Biol. & Med.* **30**:680, 1933.

EXPLANATION OF CHART 1.

Chart 1.—All the animals were given daily intraperitoneal injections of an alkaline extract of the anterior lobe of the hypophysis in doses of 2 cc. per kilogram of body weight throughout the experimental period; most of the animals also received sodium iodide.

MM, a female control animal, received only the extract. In many instances the basal metabolic rate temporarily decreased slightly below its original level after the initial cycle of hyperthyroidism was completed.

K, a female, received 0.001 Gm. of sodium iodide per kilogram of body weight simultaneously with the extract. The iodine did not affect the course of the rapidly increasing metabolic rate.

124, a male, received 0.001 Gm. of sodium iodide per kilogram of body weight simultaneously with the extract. A brief latent period permitted a slight increase in the basal metabolic rate, after which the depressant effect of the iodine became fully established.

E, a male, received 0.11 Gm. of sodium iodide per kilogram of body weight simultaneously with the extract. The iodine completely inhibited the thyreotropic activity of the extract.

EE, a male, received 0.14 Gm. of sodium iodide per kilogram of body weight simultaneously with the extract. The depressant effect of the iodine prevented the basal metabolic rate from increasing significantly until the seventh day of the experimental period, after which the extent of its influence decreased somewhat and permitted the basal metabolic rate to increase slightly. The early remission which occurred subsequent to this brief rise in the rate of metabolism may be due in part to the continued presence of the effect of the iodine and in part to an early spontaneous remission of the hyperthyroid state such as is seen not infrequently in male animals. The experiments recorded in chart 3 suggest that the myxedema level to which the basal metabolism decreased after this remission was due to the persistence of at least a small fraction of the original influence of iodine.

BB, a female, received 0.02 Gm. of sodium iodide per kilogram of body weight simultaneously with the extract. After a brief latent period during which the basal metabolic rate increased, the iodine opposed the initial thyreotropic activity of the extract, and the rate of consumption of oxygen decreased to its normal level. This remission produced by iodine, however, persisted for only five days, after which the basal metabolic rate again began to increase. This may indicate that as the depressant effect of iodine gradually became attenuated the extract correspondingly revealed more of its hitherto latent thyreotropic activity. The usual spontaneous remission finally found the thyroid gland refractory to further stimulation, and the basal metabolic rate again returned to its normal level.

If the striking decrease in basal metabolic rate which occurred subsequent to this remission is attributed to iodine (on the basis of experiments recorded in chart 3), one must postulate that iodine retains enough power to affect the thyroid gland during the phase in which it becomes refractory to the thyreotropic substance, although its influence may have become insufficient earlier in the experiment to inhibit completely the thyreotropic activity of the extract. Such a theory assumes that the thyroid gland in the postrefractory state can develop a remarkable sensitivity toward amounts of iodine which in the prerefractory state were too minute to affect its functional activity significantly. The experimental data (chart 3 and tables 2, 3 and 4) are in accord with these theoretical considerations. As a matter of fact, from the nature of the spontaneous remission, one must conclude that the physiologic state of the thyroid gland during the period in which it is potentially capable of responding to the thyreotropic substance is fundamentally different from the condition in which it subsequently finds itself refractory to this activating influence.

ever, these regressive histologic changes are fairly complete, although the reaccumulated colloid is relatively poor in iodine.⁹

During long continued daily injections of anterior pituitary extract it has been noted in several instances that a recrudescence of this cycle of hyperthyroidism occurs after a refractory interval of approximately thirty days.³

A few animals (about 8 per cent of those studied) were resistant to the thyreotropic effects of the extract and revealed a highly curtailed initial increase in the rate of metabolism and a strong tendency toward an early remission.⁷ Occasionally, a brief transitory secondary increase in the rate of metabolism occurred after such an aborted response. On the contrary, there were other animals, even less in number, which displayed only a negligible resistance to the extract, and after a rapid initial increase in the rate of consumption of oxygen these animals suffered several marked secondary exacerbations of the metabolic dis-

TABLE 1.—*Influence of Sex on the Thyreotropic Activity of an Alkaline Extract of the Anterior Lobe of the Hypophysis*

Maximum Basal Metabolic Rate, per Cent	All Animals, Percentage	Male Guinea-Pigs, Percentage	Female Guinea-Pigs, Percentage
Between +22 and +30.....	60	70	13.3
Between +31 and +66.....	40	30	86.7

turbance, which in one instance extended over a period of three months before the animal died accidentally.⁷

Sex may be one of the factors which play a rôle in the variable response which the thyreotropic activity of the extract elicits. Although not an invariable occurrence, the metabolic disturbance appeared to be more intense and of longer duration in female than in male guinea-pigs.⁶

The Thyroid Gland and the Basal Metabolic Rate in Exophthalmic Goiter.—The cycle of events which the thyreotropic substance of the anterior lobe of the hypophysis evokes in the thyroid gland of the guinea-pig is remarkably similar to that recorded as occurring in the thyroid gland in cases of exophthalmic goiter in man by Marine and Lenhart,¹⁰ Wilson¹¹ and others.

9. Schockaert, J. A., and Foster, G. L.: Influence of Anterior Pituitary Substances on the Total Iodine Content of the Thyroid Gland in the Young Duck, *J. Biol. Chem.* **95**:89, 1932. Closs, K.; Loeb, L., and MacKay, E. M.: The Effect of an Acid Extract of the Anterior Pituitary on the Iodine Concentration of the Blood and Thyroid Gland, *ibid.* **96**:585, 1932.

10. Marine, D., and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter, *Arch. Int. Med.* **8**:265 (Sept.) 1911.

11. Wilson, L. B.: The Pathology of Nodular (Adenomatous?) Goiters in Patients with and in Those Without Symptoms of Hyperthyroidism, in *Collected Papers of Mayo Clinic*, Philadelphia, W. B. Saunders Company, 1922, vol. 14, p. 434.

Marine and Lenhart recognized an early developmental stage with the parenchymal hypertrophy and hyperplasia "characteristically" found in cases of exophthalmic goiter and a later involuntary or colloid phase.

Wilson described this cycle of histopathologic change somewhat as follows: (1) an early stage, with moderate enlargement of the thyroid, marked hypertrophy and moderate hyperplasia of the parenchymal cells and diffuse hyperemia; (2) an advanced stage, with marked enlargement of the thyroid, advanced parenchymal hypertrophy and hyperplasia, loss of colloid and diffuse hyperemia, and (3) a late stage, with beginning or well marked storage of colloid, decreasing hypertrophy and hyperplasia of parenchymal cells and less hyperemia. Many follicles containing colloid during the third phase of the cycle were found to be lined with flattened acinar cells.

The clinical course of the basal metabolic rate in cases of exophthalmic goiter is also similar to the cyclic type described for experimental hyperthyroidism caused by administration of an extract of the anterior lobe of the hypophysis. Many cases are marked by a progressive intensification of the metabolic disturbance until a maximum increase or crisis is reached, after which (if the patient survives) there is a period of sustained activity which spontaneously subsides over a variable number of weeks or months. There are also more chronic cases which pursue a self-limited, irregular, less intense course with a number of remissions and exacerbations.¹²

Wilson¹¹ indicated that there is a correlation between the cycle of histopathologic changes in the thyroid gland and the behavior of the basal metabolic rate in cases of exophthalmic goiter. His findings are similar to those recently published by me³ for experimental hyperthyroidism caused by the administration of an extract of the anterior lobe of the hypophysis.

DEPRESSION OF THE FUNCTIONAL ACTIVITY OF THE THYROID GLAND

Behavior of the Basal Metabolic Rate After Simultaneous Administration of Sodium Iodide and the Thyreotropic Principle.—The usual increase in basal metabolic rate which is produced by the thyreotropic activity of the extract of the anterior lobe of the hypophysis may be partially or completely inhibited by simultaneous injections of sodium iodide.¹³

In general, this inhibitory influence exerted by iodine is marked by wide individual variations, but within certain fairly well defined limits

12. Barker, L. F.: Exophthalmic Goiter, *Internat. Clin.* 1:1, 1924. Footnote 1b, d and e.

13. Footnotes 5 and 6.

relatively large doses of sodium iodide (from 0.1 to 0.2 Gm. per kilogram of body weight) were commonly found to be more effective than relatively small doses (from 0.0001 to 0.002 Gm. per kilogram of body weight) either in totally abolishing the expected rise in basal metabolic rate or in partially inhibiting the extent of its increase.

TABLE 2.—*Effect of Large and Small Doses of Sodium Iodide on the Thyreotropic Activity of an Alkaline Extract of the Anterior Lobe of the Hypophysis**

Experimental Conditions	Increase in Basal Metabolic Rate				
	First Through Fifth Day, Over +15 per Cent	Sixth Through Tenth Day, Over +25 per Cent	Eleventh Through Fifteenth Day		
			Over +30 per Cent	Over +10 per Cent	Under +10 per Cent
Controls which received only injections of 2 cc. of anterior lobe pituitary extract.....	92.0	70.0	25.0	75.0	25.0
Guinea-pigs which received injections of the extract plus from 0.1 to 0.2 Gm. of sodium iodide per kilogram of body weight.....	23.5	11.7	0	53.8	46.2
Guinea-pigs which received injections of the extract plus from 0.0001 to 0.002 Gm. of sodium iodide per kilogram of body weight.....	72.2	61.1	38.4	84.6	15.4

* In addition to the more obvious differences in response elicited by large and small doses of sodium iodide, note particularly the unfavorable influence which the smallest doses of sodium iodide exerted on the course of hyperthyroidism induced by an extract of the anterior lobe of the pituitary from the eleventh to the fifteenth day of the experimental period.

TABLE 3.—*Range of Effective Doses of Iodide When It Is Administered to Guinea-Pigs Simultaneously with 2 cc. of Anterior Lobe Pituitary Extract Per Kilogram of Body Weight**

Effect on Basal Metabolic Rate Ordinarily Increased by Anterior Lobe Pituitary Extract	Dose of Sodium Iodide per Kg. of Body Weight, Gm.	Seventeen Animals in Series (10♂; 7♀), Percentage	Dose of Sodium Iodide per Kg. of Body Weight, Gm.	Six Animals in Series (1♂; 5♀), Percentage	Dose of Sodium Iodide per Kg. of Body Weight, Gm.	Eighteen Animals in Series (7♂; 11♀), Percentage
Complete inhibition of increase.....	0.1 to 0.2	41 (5♂; 2♀)	0.005 to 0.090	0	0.0001 to 0.002	5.5 (0♂; 1♀)
Partial inhibition of increase.....	0.1 to 0.2	29.5 (3♂; 2♀)	0.005 to 0.090	100 (1♂; 5♀)	0.0001 to 0.002	33.3 (3♂; 3♀)
No effect on the expected increase.....	0.1 to 0.2	29.5 (2♂; 3♀)	0.005 to 0.090	0	0.0001 to 0.002	61.2 (4♂; 7♀)

* This table emphasizes the value of relatively large doses of sodium iodide as compared with minute amounts. These data also indicate that the remission produced by iodine is not an all-or-none phenomenon. The influence of sex on the remission produced by iodine cannot be judged on such limited data. It is interesting, however, to note the preponderance of male animals among those deriving the maximum benefit from the largest doses of sodium iodide.

The dose of iodine apparently also plays an important rôle in the duration of its efficacy. Sodium iodide in doses of from 0.1 to 0.2 Gm. per kilogram of body weight produced earlier evidence of its depressant effect and maintained its influence over a longer period than did doses under 0.1 Gm. per kilogram of body weight. This is probably not the only factor involved, however, for it does not explain why certain animals were refractory even to the largest doses of sodium iodide given in these experiments.

The increase in the rate of metabolism which occurred in many of the animals in this series subsequent to an initial period of depression testifies to the transitory character of the remission produced by iodine and to the constant potential stimulus which the anterior lobe pituitary extract maintains during the period that its active influence is temporarily usurped by the iodine. Indeed, the detailed data indicate that the salient characteristic of this depressant effect of iodine is its temporary duration.⁶ The efficacy of iodine is most marked between the fifth and the tenth day of the experimental period. Its depressant effect, however, may persist in some measure over a variable period extending from a few days to two or three weeks.

Furthermore, the direction in which the rate of metabolism is influenced by iodine if it is given in combination with anterior lobe pituitary extract becomes obvious when the contours of the metabolic curves resulting from such experiments are compared with those for control animals which have received only the glandular extract. Such data indicate that the general behavior of the basal metabolic rate after the simultaneous administration of iodide and anterior lobe pituitary extract depends for the most part on the duration and location of the period over which the transitory depressant effect of iodine impresses itself on the cycle of hyperthyroidism caused by the administration of an extract of the anterior lobe of the hypophysis. For instance, if the effective period of the remission produced by iodine is shorter than the cycle of increased metabolism produced by a thyreotropic effect of the extract, the rate of consumption of oxygen finally increases within limits which are probably determined for a given point in the experimental period partially by the natural susceptibility of the animal to the extract and partially by the dose of iodine administered. A significant increase in the rate of metabolism, on the other hand, does not occur at any time during the experimental period if iodine depresses the metabolic disturbance until such time as the thyroid gland ordinarily becomes refractory to the thyreotropic effects of the extract. And finally, the basal metabolic rate descends to the level of hypothyroidism or myxedema in certain guinea-pigs when the depressant influence of iodine extends beyond the period during which the anterior lobe pituitary extract is capable of exerting its thyreotropic activity (*EE* and *BB*,

chart 1; chart 2 *F*). All the animals which experienced a temporary iodine remission with a secondary increase in the rate of metabolism subsequently revealed a progressive decrease in the rate of consumption of oxygen which was entirely similar to the spontaneous remission seen in guinea-pigs receiving only extract of the anterior lobe of the hypophysis.

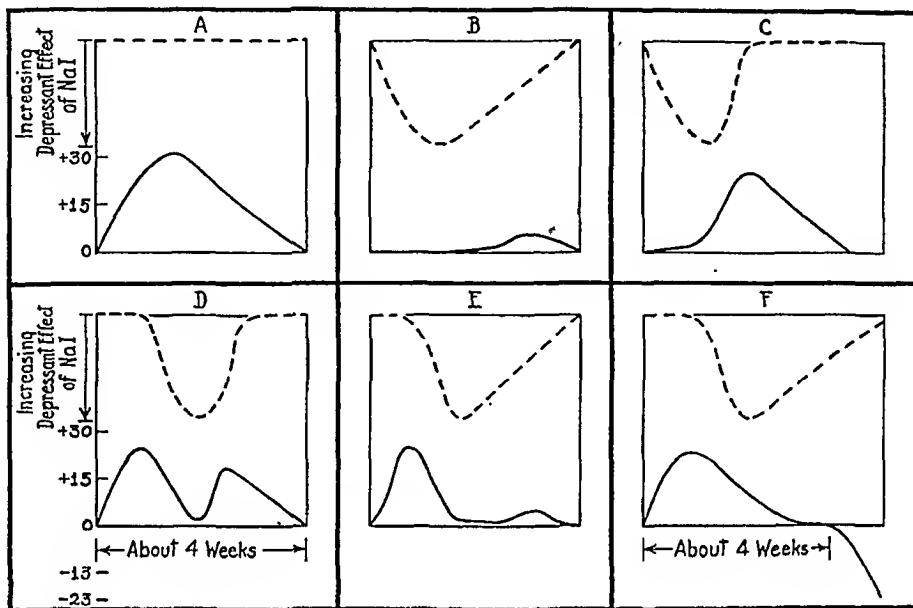


Chart 2.—The lower curves, which are represented by the solid lines, depict the actual course of events (the direction, extent and duration of percentage changes in the basal metabolic rate) in individual guinea-pigs after the simultaneous administration of iodide and anterior lobe pituitary extract. (Refer to figure 1 for the source of this material.)

The upper dotted lines signify the manner in which iodides probably exert their depressant influence in order to cause the changes in the basal metabolic rate which are so characteristic of the remission produced by iodine.

A shows that the iodine was entirely ineffective; the thyreotropic activity of the extract was therefore unopposed (compare with chart 1, *K ♀*).

B shows that the iodine exerted its depressant influence over a period which included the entire cycle of hyperthyroidism; the thyreotropic activity of the extract was therefore inhibited (*E*, chart 1). Certain experiments (*EE*, chart 1) indicate that the rate of metabolism may increase slightly if the depressant effect of the iodine becomes weakened considerably toward the end of its period of influence.

C, *D* and *E* show that the time of onset, the duration and the extent of the depressant effect of iodine play an important rôle in determining the behavior of the basal metabolic rate in these instances (*EE*, *BB* and *124*, chart 1). Note the slight tendency to a late increase in the rate of consumption of oxygen which may occur after the iodine relinquishes most of its depressant power.

In *F*, special attention is directed to the sequence of events which probably results when the effect of iodine persists beyond the period during which the extract maintains its thyreotropic activity. This interpretation has been substantiated by the experiments recorded in chart 3 (also *EE* and *BB*, chart 1).

Effect of Iodides in Exophthalmic Goiter.—The remission produced by iodine in cases of exophthalmic goiter in man is likewise a temporary phenomenon which ordinarily attains its maximum influence by the fifth to the tenth day, after which the basal metabolic rate usually increases more or less rapidly to equal or surpass its original level within the following few weeks.¹⁴

Means¹⁵ has suggested that the excessive height to which this secondary rise in metabolic rate sometimes attains is evidence of an increasing intensity of the malady rather than an expression of the transitory duration of the depressant influence of iodine. Although this is an important possibility, the "postiodine" phenomenon might also be attributed to the fact that the administration of iodine not only depresses the functional activity of the thyroid gland but simultaneously replenishes its depleted store of thyreoglobulin.¹⁵ As a result of this increase in the hormone content of the thyroid gland, the gland becomes capable of releasing its active secretion in larger quantities per unit of time at the termination of the limited period during which iodine depresses its functional state.

In some instances of mild exophthalmic goiter, iodides produce an unusually prolonged remission.¹⁶ The experimental data from cases of hyperthyroidism produced by administration of an extract of the anterior lobe of the hypophysis suggest that the cycle of hyperthyroidism has approached close enough to its period of natural remission to permit overlapping of the remission produced by iodine and the spontaneous remission.

*Effect of Iodides and Anterior Lobe Pituitary Extract (Thyroid-Stimulating Factor) on the Basal Metabolism After the Spontaneous Remission in Animals Which Have Previously Received Injections of the Extract.*¹⁷—The maximum decrease in the basal metabolic rate was recorded in individual instances as 8 per cent below the normal level

14. Footnote 1a, b, c and d.

15. Gutman, A. B.; Benedict, E. M.; Baxter, B., and Palmer, W. W.: The Effect of Administration of Iodine on the Total Iodine, Inorganic Iodine and Thyroxine Content of the Pathological Thyroid Gland, Tr. Am. A. Study Goiter, 1932; J. Biol. Chem. **97**:303 (July) 1932.

16. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, Arch. Int. Med. **45**:481 (April) 1930.

17. This experiment was originally devised to investigate the theory that depletion of the reserve of iodine in the thyroid gland is responsible for the diminishing output of its active secretion during the spontaneous remission. The results which were obtained cast doubt on this possibility and at the same time yielded further evidence of the limited period during which iodine was capable of influencing the functional behavior of the thyroid gland.

at the completion of the spontaneous remission in guinea-pigs which had received injections of only the anterior lobe pituitary extract.⁷ Thereafter, the simultaneous administration of sodium iodide and anterior lobe pituitary extract (thyroid-stimulating factor) resulted in a further depression of the basal metabolic rate¹⁸ to hypothyroid and myxedematous levels. The detailed data indicate that the depressant effect of iodine was merely temporary and that the basal metabolic rate in these experiments decreased progressively to reach its lowest level usually by the fourth day, after which there was a gradual increase in the rate of consumption of oxygen over a period of from one to more than three weeks before the original level was attained.

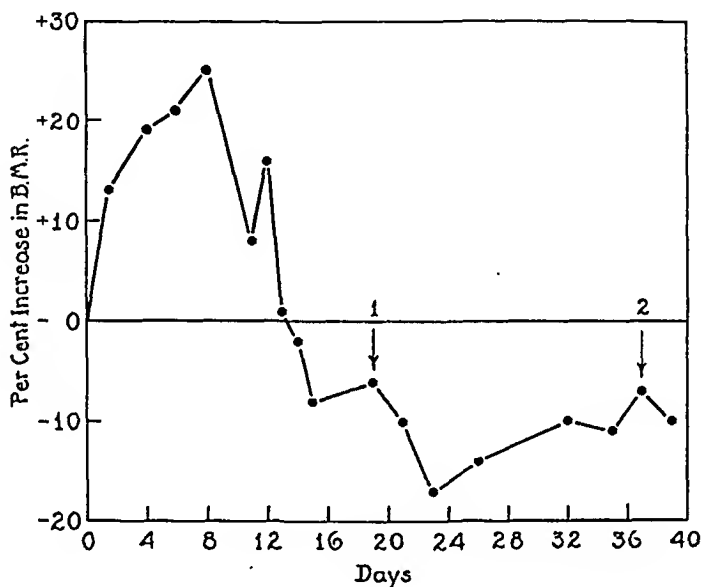


Chart 3.—This curve is composed of averaged data and is based on the 5 guinea-pigs to which reference is made in table 4.

The arrow at 1 indicates that daily injections of 0.0005 Gm. of sodium iodide per kilogram of body weight were combined with the anterior lobe pituitary extract which had previously been given alone for a period of nineteen days.

The arrow at 2 points to the time at which the dose of sodium iodide was increased to 0.175 Gm. per kilogram of body weight. The resultant decrease in the basal metabolic rate occurred in only 1 animal (from minus 13 to minus 23 per cent), while no change in the rate of metabolism was detected in the other 4 animals.

Effect of Iodides on the Basal Metabolism of Normal Rabbits.—

There is a striking similarity between the results of the latter experiments and those reported by Webster and Chesney¹⁹ and Marine, Deutch

18. Friedgood, H. B.: Studies on the Nature of the Spontaneous Remission in Experimental Exophthalmic Goiter of Guinea-Pigs, to be published.

19. Webster, B., and Chesney, A. M.; Endemic Goitre in Rabbits: III. Effect of Administration of Iodine, Bull. Johns Hopkins Hosp. 43:291, 1928.

and Cipra²⁰ for the effect of iodides on the basal metabolic rate of normal rabbits. The time relations of the temporary decrease in the rate of consumption of oxygen and the period required for its recovery are almost identical in the three series of experiments. While the ultimate significance of this parallelism may not be apparent at present, the point of immediate interest is the transitory duration of the effect of the iodide in each instance.

TABLE 4.—*Temporary Effect of Iodide on the Basal Metabolic Rate of Normal Rabbits and on the Basal Metabolic Rate of Guinea-Pigs After the Spontaneous Remission*

Identification of Animal			Maximum Depression in Basal Metabolic Rate, Percentage			Day of Experimental Period on Which Maximum Depression Occurred			Day of Experimental Period on Which Basal Metabolic Rate Returned to Original Level		
Guinea-Pig (This Series)	Rabbit (Webster and Chesney)	Rabbit (Marine, Deutch and Cipra)	This Series*	Webster and Chesney†	Marine, Deutch and Cipra‡	This Series	Webster and Chesney	Marine, Deutch and Cipra	This Series	Webster and Chesney	Marine, Deutch and Cipra
125 ♂	2083	589B ♀	—24	—25	—22	4th	3d	3d	18th	30th	13th
127 ♂	2038	616 ♀	—22	—19	—22	7th	4th	3d	18th (still —13%)	30th§ (still —29%)	9th (still —15%)
128 ♂	2061	622 ♀	—20	—19	—21	4th	3d	1st	7th	6th	13th (still —8%)
122 ♂	2037	605 ♀	—17	—16	—18	4th	3d	7th	20th (still —13%)	Between 15th and 30th	9th (still —17%)
120 ♂	2036	604 ♀	—14	—11	—15	4th	2d	3d	13th	5th	13th (still —17%)§

* See chart 3 for a composite curve. The five guinea-pigs were given anterior lobe pituitary extract for nineteen days until the expected cycle of hyperthyroidism was completed. At this point sodium iodide was included in the daily injections (0.0005 Gm. per kilogram of body weight). The first day of the experimental period on which this table is based was the nineteenth day of the injections of anterior lobe pituitary extract.

† All of six animals responded with a decrease in metabolism. The percentage values were calculated from published data.

‡ Five of eighteen animals responded with a decrease in metabolism. The percentage values were calculated from published data.

§ Secondary depression.

EFFECT OF IODINE ON THE HISTOLOGIC APPEARANCE OF THE NORMAL THYROID GLAND

Gray and Loeb,²¹ Rabinovitch²² and Irsigler²³ have demonstrated that the daily intraperitoneal injections of potassium iodide in guinea-pigs and rats result in a rapid increase in the rate of mitotic prolifera-

20. Marine, D.; Deutch, M., and Cipra, A.: The Effect of Large Doses of Iodine on Heat Production in Rabbits, *Proc. Soc. Exper. Biol. & Med.* **24**:657, 1927.

21. Gray, S. H., and Loeb, L.: The Effect of the Oral Administration of Potassium Iodide and Thyroid Substance on the Mitotic Proliferation and Structure of Acini in the Thyroid Gland in Guinea Pigs, *Am. J. Path.* **4**:257, 1928.

tion of the thyroid epithelium. The maximum effect occurs by the tenth day, at which time the number of mitoses has increased from its original level of about 200 to a maximum count of approximately 6,000 per gland (guinea-pig). The number of mitoses then begins to decrease between the tenth and the fifteenth day and practically returns to normal by the twentieth day, although the daily administration of iodide is continued uninterruptedly. A slight transient secondary rise may occur after the thirtieth day.

The oral administration of potassium iodide appears to modify the time factor in this response so that the peak of the effect of the iodide does not occur until from the fifteenth to the twentieth day, after which the number of mitoses decreases rapidly. Proliferation ceases after the thirtieth day. In addition to this temporary increase in the rate of mitosis, there are also moderate changes in the appearance of the colloid, which tends to become softer, and in the epithelium, which assumes a medium cuboid height, especially after intraperitoneal administration of iodide.

Kuschinsky²⁴ (confirmed by Loeser²⁵) proved that these changes in the thyroid gland were produced indirectly through the anterior lobe of the hypophysis. He also demonstrated that the direct effect of iodine on the anterior lobe of the hypophysis was temporary and persisted for the same period that had been observed for the duration of its indirect effect on the thyroid gland. The functional significance of these histologic changes which are produced in the thyroid gland by virtue of the effect of iodine on the anterior lobe of the hypophysis is still to be established.

COMMENT

The data of the present investigation indicate that the response of the thyroid gland to stimulation depends, first, on the type of stimulus to which it is subjected and, second, on another factor which prevents

22. Rabinovitch, J.: The Effect of Feeding Potassium Iodide on the Proliferative Activity of the Thyroid Gland in Guinea Pigs, *Am. J. Path.* **4**:601, 1928; The Effect of Intraperitoneal Injection of Potassium Iodide on the Proliferative Activity of the Thyroid Gland in Guinea Pigs, *ibid.* **5**:91, 1929; Changes in the Thyroid Gland of the Guinea Pig Following a Period of Administration of Potassium Iodide, *ibid.* **6**:71, 1930; Effect of Intraperitoneal Injections of Potassium Iodide on Proliferative Activity of Thyroid Gland in Rats, *Proc. Soc. Exper. Biol. & Med.* **28**:394, 1931.

23. Irsigler, F. H.: Die Wirkung intraperitonealer und peroraler Jodkaligaben auf die Rattenschilddrüse, *Beitr. z. path. Anat. u. z. allg. Path.* **85**:221, 1930.

24. Kuschinsky, G.: Ueber die Bedingungen der Sekretion des thyreotropen Hormons der Hypophyse, *Arch. f. exper. Path. u. Pharmakol.* **170**:510, 1933.

25. Loeser, A.: Umstimmung der Schilddrüsentätigkeit durch Jod, *Klin. Wchnschr.* **13**:533 (Jan. 20) 1934.

it from responding indefinitely to the demands of any stimulus. The period during which the thyroid gland can be maintained in an abnormal physiologic state is therefore consistently limited.

Excitant and depressant stimuli induce a cycle of activity which is characterized by a departure of the gland from its normal functional level in a direction governed by the nature of the stimulus, e. g., hyperactivity or hypo-activity. After a maximum change from the initial physiologic state has been achieved and the rate of activity of the thyroid gland has been either significantly increased or decreased, a spontaneous remission occurs. The return toward the original functional level progresses in spite of, or because of, the continued presence of the stimulus. In certain instances, there is also a tendency for this regression to swing slightly beyond the initial point of departure into the opposite physiologic state, i. e., from hyperthyroidism to hypothyroidism.

These well defined relationships between stimulus and response may become somewhat more complicated if the functional activity of the thyroid gland is, to begin with, in an abnormal state (e. g., the effect of iodine on the established hyperthyroidism in cases of exophthalmic goiter and on the experimental hyperthyroidism due to extract of the anterior lobe of the hypophysis). In such instances there is apparently a summation of the two opposite forces. The result depends not only on the relative influence on the thyroid gland of the opposing stimuli but on the manner in which their transitory cycles of activity overlap (chart 2).

The total time required by the thyroid gland of the guinea-pig to negotiate its complete cycle following stimulation varies from two to about four weeks. However, the maximum deviation from the normal functional level is usually attained by the seventh day of the experimental period.

The cyclic response of the thyroid gland to stimulation may be an inherent characteristic of its physiologic organization. This does not appear to be true, however, for the effect of iodides on the histologic appearance of the thyroid gland. Kuschinsky's investigations²⁴ certainly indicate that the anterior lobe of the hypophysis plays an important rôle in determining the character and duration of this effect of iodide. A similar extrathyroid mechanism for controlling the unbridled activity of the thyroid gland remains a possible explanation for the refractory state which develops during the administration of the thyreotropic principle.⁷

Careful experiments indicate that this remission is not due to a progressive decrease in the potency of the extract.³ Although there are several obvious possibilities, no cleancut evidence is as yet available to permit a final judgment in the matter.

Several experiments (chart 3) which were devised to limit the number of these possibilities suggest that depletion of the reserve of iodine in the thyroid gland is probably not responsible for this phenomenon, while other data¹⁸ have established that the spontaneous remission is not due to inactivation of the thyroid hormone or to interference with peripheral oxidation but may be directly attributed to a decrease in the output of the calorigenic hormone from the thyroid gland.

Collip and Anderson²⁶ have recently published evidence on the production of a serum which is inhibitory to the so-called thyreotropic hormone. Their experimental data are convincing, but the conception of an antihormone by which they attempt to explain their results can be accepted only with reservation at the present time.

The chemically crude protein-containing extracts now in use suggest that the development of a specific antibody might directly neutralize or inactivate the injected anterior lobe pituitary extract. Furthermore, iodine is known to be a powerful antagonist of the thyreotropic activity of such extracts. It seems reasonable, therefore, to withhold final judgment on their antihormone theory until further work establishes, among other things, first, whether the antagonistic substance which they have encountered is active against similar extracts prepared from several species of mammal or whether it is specifically potent only against the extract which stimulates its production, and, second, that iodine itself has played no rôle in the phenomenon which they have described.

26. Collip, J. B., and Anderson, E. M.: The Production of Serum Inhibitory to the Thyrotropic Hormone, *Lancet* 1:76 (Jan. 13) 1934.

NORMAL HEMATOLOGIC STANDARDS

EDWIN E. OSGOOD, M.D.

PORTLAND, ORE.

This paper presents a summary of the results of a series of hematologic studies, including all the commonly used procedures, on over 500 healthy persons of both sexes ranging from young children to adults. Details of these studies¹ together with reviews of the literature will appear elsewhere. The development of a uniform system of methods for the hematologic study of oxalated venous blood made this investigation possible. These methods are simple enough for routine clinical use, but they approach research methods in accuracy. Erythrocyte counts, hemoglobin values, hemoglobin coefficients and color indexes are reported for 626 persons; cell volumes, volume coefficients and volume and saturation indexes, for 583; reticulocyte counts, for 476; leukocyte and differential counts, for 597, and sedimentation rates, for 853. The ages of the subjects ranged from 4 years to past 30.

SUBJECTS

All the subjects lived in or near Portland, Ore., at an elevation of less than 500 feet (152.4 meters). All were white and native-born, in most instances of native-born parents. Most of the men were medical students and a few were physicians; the women were for the most part nurses, with a few laboratory technicians and medical students. The boys aged from 14 to 19 and the girls from 14 to 17 were high school students. The children were from the public graded schools,² orphan asylums,² baby homes, physicians' families and the outpatient clinic. The children of the outpatient clinic had been brought in for tonsillectomy but were found by the examining physician to present no indications for this operation. The results obtained for persons of the different social classes were at first averaged separately, but no significant differences were found. All the subjects had had a recent physical examination, and they stated at the time the blood was taken that they felt perfectly well. Tests giving atypical results were repeated, and the patient was reexamined in many instances, but unless a reason was found other than the results of one of the hematologic tests, the subjects were not excluded from the series.

From the Department of Medicine, University of Oregon Medical School.

Read before the Section on Pathology and Physiology at the Eighty-Fifth Annual Session of the American Medical Association, Cleveland, June 14, 1934.

1. Mrs. Mable Wilhelm Osgood, Mr. Russell L. Baker and Miss Inez Brownlee collaborated in these studies.

2. Dr. Helen Cary and Dr. Frank Mount cooperated in securing suitable subjects from the schools and orphan asylums.

It seems justifiable to regard these subjects as representative of the healthy³ white population of the Pacific Northwest. There is considerable evidence (table 1) that data derived from such subjects are applicable to those from other parts of this country and from Europe.

METHODS

Since the methods have been described in detail elsewhere,⁴ they will be commented on briefly here. Venous blood containing 2 mg. of dry potassium oxalate

TABLE 1.—*Mean Hematologic Values for Persons of Different Localities**

Locality	Men				Women			
	Num-ber of Sub-jects	Red Cells, Millions per C.Mm.	Hemo-globin,† Gm. per 100 Cc.	Volume of Packed Red Cells,‡ Cc. per 100 Cc.	Num-ber of Sub-jects	Red Cells, Millions per C.Mm.	Hemo-globin,† Gm. per 100 Cc.	Volume of Packed Red Cells,‡ Cc. per 100 Cc.
United States, East Groups I and II.....	61	5.40	15.8	46.6	73	4.78	14.0	41.5
United States, Midwest Groups I and II.....	7	5.50	16.1	47.0	15	4.89	14.3	43.1
United States, West Groups I and II.....	2	5.56	16.0	48.2	2	4.70	14.1	41.5
United States, South Groups I and II.....	16	5.40	15.6	45.7	11	4.85	14.1	43.0
United States, Midwest Haden.....	70	4.95	15.3		30	4.38	13.4	
United States, Midwest Haden.....	40	4.97	15.5	45.8	12	4.26	13.3	39.0
United States, East Emerson.....	171	5.44	15.1					
United States, West Osgood.....	137	5.39	15.8	46.4	100	4.80	13.7	42.4
United States, South Wintrobe.....	100	5.85	17.0	49.6	50	4.93	13.8	41.5
Various parts of the world	310±	5.50	16.2	46.0	210±	4.78	13.9	41.0
United States, South Poster and Johnson...	40	5.26	15.7	46.7				
Denmark Gram and Norgaard...	10	5.45	15.0	46.3	10	4.65	13.0	40.5
Denmark Bie and Möller.....	10	5.53	14.3	46.4	10	4.74	13.3	38.7
Germany Horneffer.....	40	4.96	16.0					
England, London Price-Jones.....	100	5.43	14.9		100	5.01	13.9	
Average for entire series...	477±	5.43	15.9	47.7	369±	4.85	13.9	41.8

* Reproduced by permission of Wintrobe, M. M. (Blood of Normal Men and Women, Bull. Johns Hopkins Hosp. 53 : 118 [Sept.] 1933).
† Corrected to correspond to values obtained by the Van Slyke method.
‡ Corrected to correspond to the volume of packed red cells in heparinized blood.

3. Many reports of so-called normal values have been based on studies of patients with minor illnesses in clinics or hospitals. This practice is to be condemned. It probably accounts for some of the differences between the standards determined by my associates and me and those in general use.

4. (a) Osgood, E. E.; Haskins, H. D.; Trotman, F. E., and Mathieu, A.: A Uniform System of Hematologic Methods for Use with Oxalated Venous Blood; A Simplification of the Osgood-Haskins Hemoglobin Method; A Rapid Method for Determination of the Sedimentation Rate of the Red Cells with Results in Health and Disease, J. Lab. & Clin. Med. 16:476 (Feb.) 1931. (b) Osgood, E. E.: A Textbook of Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Co.,

per cubic centimeter was used for all the determinations and is recommended for use as a routine because of its convenience and the greater accuracy of the results. No difficulty was encountered in obtaining blood from a vein, even with the younger children. The blood was taken at any time of the day, as in ordinary office practice.

Red cell counts were made with apparatus certified by the Bureau of Standards, Toisson's diluting fluid⁵ being used. Two or more counts made on separate dilutions agreeing to within 100,000 cells per cubic millimeter were averaged.

Leukocyte counts were made in the usual manner, the average of two counts agreeing to within 1,000 cells being recorded.

Estimations of hemoglobin were made with the care employed for research by the method of Osgood and Haskins,⁴ for the determination of hemoglobin,⁶ which, although a simple clinical procedure, has been shown⁷ to give results comparable in accuracy to the methods of Van Slyke for the determination of the oxygen capacity or the iron of the blood. Results are expressed both in grams per hundred cubic centimeters and in percentages, 100 per cent by this method being equivalent to 13.8 Gm. per hundred cubic centimeters. The cell volume was determined by centrifugation to constant volume in my cell volume tube.⁸ Correction for shrinkage due to the oxalate should be made by the addition of 3.5 per cent of the volume of packed cells if one wishes to compare the results with those obtained with isotonic anticoagulants, but this is not necessary if one uses oxalated blood.

Hemoglobin and volume coefficients were calculated in the usual way,^{4b} and color, volume and saturation indexes were computed from the average coefficients determined for the sex and age group to which the subject belonged. Corpuseular hemoglobin, corpuseular volume and concentration of corpuseular hemoglobin were computed according to the method of Wintrobe.⁹

The differential cell counts represent the average of two counts of 100 cells each checked with each other. These were made from the thin ends of blood smears stained with Wright's stain, a buffer solution of phosphate^{9a} with a pH of 6.4 being used instead of water.

ed. 2, 1935, pp. 192 and 378; Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women, *Arch. Int. Med.* **39**:643 (May) 1927. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards, *ibid.* **37**:685 (May) 1926; Tables for Calculation of Color Index, Volume Index and Saturation Index Based on Recently Determined Standards, *J. Lab. & Clin. Med.* **12**:899 (June) 1927. Osgood, E. E., and Wilhelm, Mable M.: Reticulocytes, *ibid.* **19**:1129 (July) 1934. Osgood, E. E.; Baker, R. L., and Wilhelm, Mable M.: Reticulocyte Counts in Healthy Children, *Am. J. Clin. Path.* **4**:292 (May) 1934.

5. Osgood,^{4b} p. 408.

6. The standard is obtainable from Hynson, Westcott and Dunning, Inc., Baltimore.

7. Dowden, C. W.; McNeill, C., and McNeill, J. D.: A Clinical Study of Blood Iron and Hemoglobin, *J. Lab. & Clin. Med.* **19**:362 (Jan.) 1934.

8. The cell volume tube is obtainable from the Arthur H. Thomas Company, Philadelphia.

9. Wintrobe, M. M.: Size and Hemoglobin Content of the Erythrocyte, *J. Lab. & Clin. Med.* **17**:899 (June) 1932.

9a. Osgood,^{4b} p. 411.

Reticulocyte counts were made by mixing 5 drops of oxalated blood with 5 drops of a 1 per cent solution of brilliant cresyl blue in an 0.85 per cent solution of sodium chloride and allowing the suspension to stand one minute or longer. A thin smear was made, and all the reticulocytes occurring among 1,000 consecutive erythrocytes were enumerated and the percentages calculated. Total reticulocyte counts were not determined, since Osgood and Wilhelm^{4b} have shown that they are of little significance.

The determinations of the sedimentation rate^{4b} were made by reading at the end of fifteen and forty-five minutes the number of millimeters that the cells had settled from a column of oxalated blood in a pipet¹⁰ containing 1 cc. of blood at a point 200 mm. from the tip and graduated in millimeters from this point to the tip. This method has all the advantages of the Westergren method and of the graphic method of Cutler; it is simpler and more rapid and uses the same oxalated blood employed for other hematologic methods.

All the determinations were made by persons highly skilled in the use of the methods.¹¹

RESULTS

The results are summarized in charts 1 to 6 and in table 2. The results of my previously reported studies^{4b} are included. In addition to the average values, ranges are given which include 95 per cent of the results for healthy subjects, corresponding to a range of plus or minus about three times the probable error. There is only about one chance in twenty that a result falling outside these values is normal. It is recommended that the values within these ranges be used in interpreting results rather than those within the extreme ranges which may be seen in the charts.

It was anticipated that the results would fall into three groups: those for children, those for adolescent boys and girls and those for adults. It was found that the ages at which changes took place in the various values did not always correspond to these divisions, so normal values for each method used in the investigations are divided into groups based on sex and age (table 2) according to the observed distribution. The few subjects who were past 30 are included in the 30 year group indicated in the charts. The values given in the text and in table 2 are those recommended for clinical use; those indicated in parentheses are the actual average values.

When there were no significant differences between the sexes the results for the two sexes were averaged. Differences between the sexes

10. Arthur H. Thomas Company, catalog no. 3649-A.

11. The erythrocyte counts and determination of cell volume were made by Dr. Frank E. Trotman, Mr. Russell L. Baker and Mrs. Mable Wilhelm Osgood; the hemoglobin estimations and reticulocyte counts, by Mrs. Mable Wilhelm Osgood and me, and the leukocyte and differential counts and the determinations of the sedimentation rate, by Miss Inez Brownlee, Mr. Russell L. Baker and Mr. Howard Johnson. The calculations were all checked several times by Mrs. Mable Wilhelm Osgood, myself and others.

were found only in the values pertaining to the size and hemoglobin content of erythrocytes for persons over 13.

TABLE 2.—*Hematologic Values Obtained for Healthy Subjects in the Present and Similar Series*

	No. of Sub- jects	Age, Years	Sex	Average Values		Range of Values
				Clinical	Actual	
Erythrocyte count, millions.....	215	4-13	M & F	5.0	(5.04)	4.2-5.8
	259	14-30+	M	5.4	(5.42)	4.6-6.2
	152	14-30+	F	4.8	(4.83)	4.2-5.4
Hemoglobin, percentage.....	215	4-13	M & F	85	(85.90)	70-100
	259	14-30+	M	115	(114.82)	100-130
	152	14-30+	F	100	(100.80)	85-115
Hemoglobin, Gm.	215	4-13	M & F	12.0	(11.92)	10.0-14.0
	259	14-30+	M	15.8	(15.84)	14.0-18.0
	152	14-30+	F	13.8	(13.91)	11.5-16.0
Hemoglobin coefficient.....	215	4-13	M & F	12.0	(11.87)	10.20-13.80
	259	14-30+	M	14.7	(14.66)	12.75-16.75
	152	14-30+	F	14.3	(14.41)	12.50-16.00
Cell volume, cc. per 100 cc.	215	4-13	M & F	36	(36.02)	31-41
	46	14-17	F	36	(36.73)	31-41
	63	14-19	M	41	(40.14)	36-45
	106	18-30+	F	41	(40.96)	36-45
	153	20-30+	M	45	(44.79)	40-50
Volume coefficient.....	304	4-17	M & F	36	(36.31)	31-41
	173	18-30+	M	41	(40.29)	35-45
	106	18-30+	F	43	(42.83)	38-47
Color index.....	626	4-30+	M & F	1	(1.00)	0.85-1.15
Volume index.....	583	4-30+	M & F	1	(1.00)	0.85-1.15
Saturation index.....	583	4-30+	M & F	1	(1.00)	0.90-1.10
Reticulocytes, percentage.....	476*	4-30+	M & F	1.5	(1.46)	0.50-3.00
Leukocyte count.....	86	4-7	M & F	10,400	(10,365)	6,000-15,000
	242	8-18	M & F	8,300	(8,342)	4,500-13,500
	269	19-30+	M & F	7,400	(7,447)	4,500-11,500
Segmented neutrophils, percentage.....	241	4-14	M & F	38	(37.60)	18-58
	120	15-19	M & F	48	(47.65)	25-75
	236	20-30+	M & F	54	(54.26)	33-78
Neutrophil staff cells, percentage.....	219	4-13	M & F	3.0	(3.07)	0-10
	378	14-30+	M & F	0.8	(0.78)	0-5
Lymphocytes, percentage.....	241	4-14	M & F	48	(48.21)	21-71
	120	15-19	M & F	42	(41.91)	22-62
	236	20-30+	M & F	38	(37.76)	18-65
Monocytes, percentage.....	219	4-13	M & F	3	(3.08)	0.5-7
	378	14-30+	M & F	4	(4.18)	0-9
Segmented eosinophils, percentage.....	219	4-13	M & F	2.8	(2.79)	0-8
	378	14-30+	M & F	1.9	(1.90)	0-6
Segmented basophils, percentage.....	597	4-30+	M & F	0.5	(0.52)	0-2
Disintegrating cells, percentage.....	219	4-13	M & F	5.0	(4.89)	0-10
	378	14-30+	M & F	3.5	(3.47)	0-7
Sedimentation rate, mm. in 15 min.....	853*	4-30+	M & F	0-5
Sedimentation rate, mm. in 45 min.....	853*	4-30+	M & F	1-30

* The discrepancy between these values and those recorded on the charts is due to the fact that the ages were not recorded for some of the adults studied.

The erythrocyte counts (chart 1) average 5,000,000 (5,040,000) per cubic millimeter and range from 4,200,000 to 5,800,000 for children from 4 to 13 years of age. At the age of 14 the results for the two sexes diverge sharply, attaining rapidly the values for adults. The erythrocyte counts for males aged 14 and over average 5,400,000 (5,420,000) and range from 4,600,000 to 6,200,000; for females the

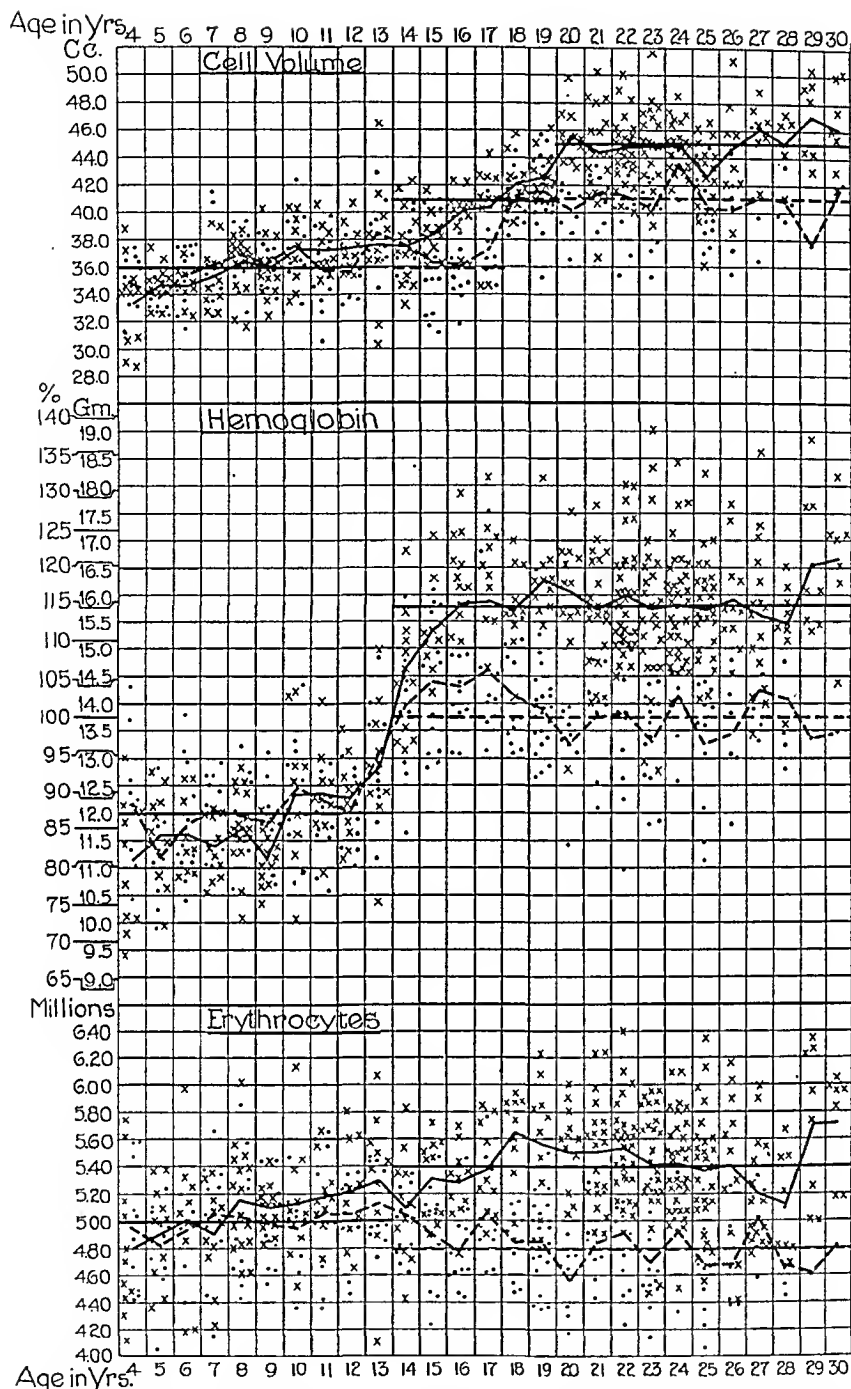


Chart 1.—Curves for the average values and the distribution of individual values for the cell volume, hemoglobin content and erythrocyte count. The values for the cell volume are expressed in cubic centimeters per hundred cubic centimeters for 328 males and 255 females; those for hemoglobin, in percentages and in grams per hundred cubic centimeters for 371 males and 255 females, and those for the number of erythrocytes in millions for persons of the same groups as those on which the studies of hemoglobin were based. In this chart and in the accompanying charts the curves for males are shown in solid lines and the individual values by crosses and the curves for females by broken lines and the individual values by dots. The values in all the studies were obtained for persons ranging in age from 4 to 30 years.

average is 4,800,000 (4,830,000), with a range of from 4,200,000 to 5,400,000. There seems to be no excuse for retaining the obsolete value of 4,500,000 for women and that of 5,000,000 for men still found in some textbooks.

The hemoglobin (chart 1) for children is lower than that for adults of either sex, averaging 12 (11.92) Gm. per hundred cubic centimeters, or 85 (85.9) per cent, and ranging from 10 to 14 Gm., or from 70 to 100 per cent. At the age of 14 the concentration of hemoglobin increases for both sexes but more markedly for boys, quickly reaching the values previously established for adults (table 1). The average value for males aged 14 and over is 15.8 (15.84) Gm., or 115 (114.82) per cent, with a range of from 14 to 18 Gm., or from 100 to 130 per cent, and for females the average value is 13.8 (13.91) Gm., or 100 per cent, with a range of from 11.5 to 16 Gm., or from 85 to 115 per cent. The only series of hemoglobin estimations for this age group of comparable size and accuracy is that of Williamson,¹² who studied 68 children of each sex aged from 4 to 15 years and 156 men and 157 women aged from 16 to 60, a total of 449 subjects compared to that of 626 reported on here. It is generally recognized that his values are accurate in relation to each other but that they are all too high.¹³ If 10 per cent is deducted from his values they agree satisfactorily with those reported here.

The hemoglobin coefficient (chart 2) is the number of grams of hemoglobin per hundred cubic centimeters of blood calculated on the basis of a red cell count of 5,000,000 per cubic millimeter. The average hemoglobin coefficient for a person of the age and sex of the subject should be used as equivalent to 100 per cent hemoglobin in calculating the color and saturation indexes. It is noteworthy that the average hemoglobin coefficient for the 215 children, 12 (11.87), is considerably lower than that for adults and that the average hemoglobin coefficient for women, 14.3 (14.41), is slightly lower than that for men, 14.7 (14.66). This means that the red cells of children contain on the average about 20 per cent less hemoglobin than those of adults. The difference between the sexes in adult life is definite but not so marked as to introduce any great clinical error if Wintrobe's⁹ suggestion of using the average value of 14.5 is followed. However, the tables for calculation^{4b} render the use of the more accurate values simple. The

12. Williamson, C. S.: Influence of Age and Sex on Hemoglobin: A Spectrophotometric Study of Nine Hundred and Nineteen Cases, *Arch. Int. Med.* **18**: 505 (Oct.) 1916.

13. Notwithstanding this fact, the Newcomer hemoglobinometer is standardized so that 100 per cent corresponds to the value of 16.92 Gm. per hundred cubic centimeters obtained by Williamson for men.

difference between the average hemoglobin coefficient for children and for men and women makes it impossible to select any one value as normal for the percentage of hemoglobin. All results for hemoglobin should be reported in grams per hundred cubic centimeters and interpreted in the light of the normal values for a person of the age and sex of the patient.

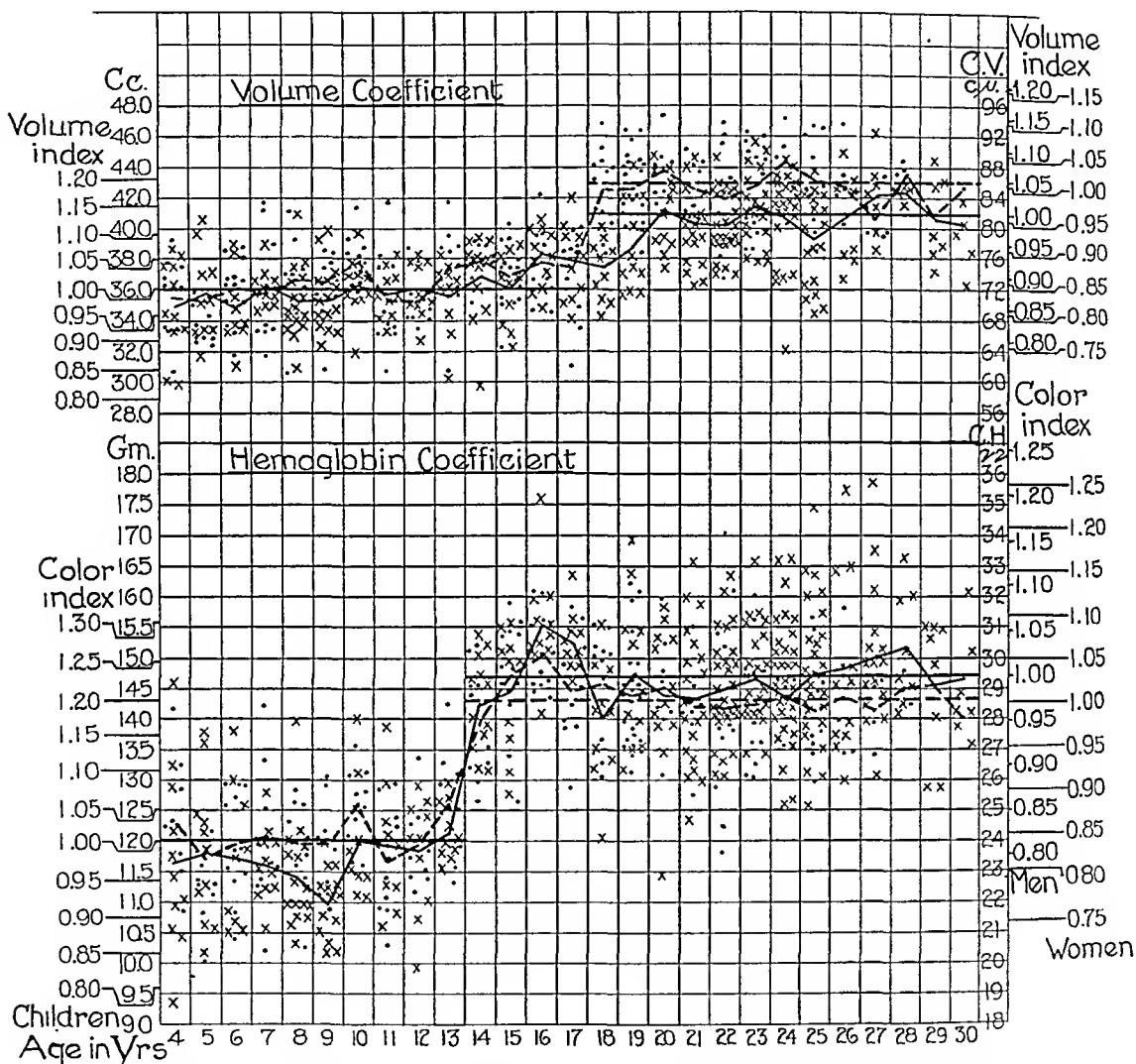


Chart 2.—Curves for the average values and the distribution of individual values for volume and hemoglobin coefficients. The values for the volume coefficient are expressed in cubic centimeters of packed cells per hundred cubic centimeters for 328 males and 255 females and those for the hemoglobin coefficient in grams per hundred cubic centimeters for 371 males and 255 females. The color and volume indexes, calculated from the hemoglobin and volume coefficients, are indicated for children and for men and women of the various age and sex groups. The corpuscular hemoglobin (C.H.), expressed in micromicrograms, and corpuscular volume (C.V.) expressed in cubic microns ($c.\mu$), are shown at the right.

The cell volume (chart 1) is expressed in cubic centimeters of packed erythrocytes per hundred cubic centimeters of blood. It is much lower, with an average of 36 cc. and a range of from 31 to 41 cc. for children aged from 4 to 13 years and for girls aged from 14 to 17 than for boys from 14 to 19 and for women from 18 to 30. For women the average cell volume is 41 cc., and the range is from 36 to 45 cc. per hundred cubic centimeters of blood. For men of 20 and past the cell volume is still higher, averaging 45 cc. with a range of from 40 to 50 cc., which corresponds to the higher red cell count for men.

The volume coefficient (chart 2) is expressed as the number of cubic centimeters of packed red cells per hundred cubic centimeters of blood calculated on the basis of a red cell count of 5,000,000 per cubic millimeter. The average normal volume coefficient for the sex and age group to which the subject belongs should be used as equivalent to a cell volume of 100 per cent in calculating the volume and saturation indexes. It is interesting to note that the cells remain small, the volume coefficients averaging 36 (36.31) with a range of from 31 to 41 until the age of 17, although the hemoglobin content of the cells increases at the age of 14. The volume coefficients for women average 43 (42.83), with a range of from 38 to 47, and for men, 41 (40.29), with a range of from 35 to 45, showing that the cells of women are slightly larger than those of men.

The color, volume and saturation indexes (chart 2) for all the ages represented and for both sexes average exactly 1 and range from 0.85 to 1.15, with the exception of the saturation index, which shows a range of from only 0.9 to 1.1. The indexes were calculated from the hemoglobin and volume coefficients determined for each sex and age group. If all the indexes had been calculated on the basis of the standards for men it is evident from chart 2 that children would have a color index of about 0.82, a volume index of about 0.88 and a saturation index of about 0.93. In other words, the erythrocytes of children are, on the average, smaller than those of adults; they contain much less hemoglobin per cell and have a somewhat lower concentration of corpuscular hemoglobin. It is also evident that the color index, the hemoglobin coefficient and the concentration of corpuscular hemoglobin are but different ways of expressing the same thing. Calculation of the color index is recommended as the simplest method for comparison.

Similarly, the mean corpuscular volume expresses the same thing as the volume index or the volume coefficient. It is the average volume of the erythrocyte expressed in cubic microns. It is interesting to note in table 2 that the saturation index shows less variation within one sex and age group than the color index. In other words, the concentration of hemoglobin per unit volume of red cells remains constant.

The average concentration of corpuscular hemoglobin may be calculated by dividing the hemoglobin, expressed in grams, by the cell volume, expressed in cubic centimeters. The result is expressed in percentages. We obtained the same value (35 per cent for men) as that given by Wintrobe.⁹ The value for women and for children aged from 4 to 13 years was 33.5 per cent, but we found higher concentrations, 38.5 and 36.5 per cent, respectively, for adolescent boys aged from 14 to 19 and girls aged from 14 to 17. This higher concentration of hemoglobin in adolescent persons, corresponding to a saturation index of 1.1 if calculated on the basis of standards for adults, has not hitherto been reported.

The availability of accurate standards for hemoglobin and volume coefficients for children should make possible a more accurate diagnosis of anemia in children, as it has in adults.¹⁴ In adults high volume and color indexes are the most conclusive evidence available that a patient has pernicious anemia or a related anemia which will respond to liver therapy, and low saturation, color and volume indexes, the best evidence that anemia is due to relative deficiency in iron (in cases of chronic hemorrhage) or to absolute (nutritional) deficiency and that the condition will respond to large doses of iron.

The average values for the erythrocyte count, hemoglobin content, hemoglobin coefficient, cell volume, volume coefficient and color, volume and saturation indexes agree well with those previously reported^{4b} for a smaller series of similar subjects and with the averages obtained by other workers in this field (tables 1 and 2).

The percentages of reticulocytes (chart 3) are the same, averaging 1.5 (1.46), with a range of from 0.5 to 3, for persons of the two sexes and all the ages included in this study. It bears no relationship to the total erythrocyte count, a fact which was not anticipated. The absolute number of reticulocytes, therefore, follows the total red cell count closely and is of little or no diagnostic value. It is recommended that reticulocyte counts be reported in percentages only. It should be noted that with the technic^{4b} used the average counts are much higher than those usually reported. When this technic is used a count of less than 0.3 per cent is a definite indication of hypofunction of the marrow, and a count of more than 4 per cent, of hyperfunction.

14. Haden, R. L.: Accurate Criteria for Differentiating Anemias, *Arch. Int. Med.* **31**:766 (May) 1923. Osgood, E. E.; Haskins, H. D., and Trotman, F. E.: The Value of Accurately Determined Color, Volume and Saturation Indexes in Anemias, *J. Lab. & Clin. Med.* **17**:859 (June) 1932. Osgood, E. E., and Haskins, H. D.: Causes, Classification and Differential Diagnosis of Anemias, *Ann. Int. Med.* **5**:1367 (May) 1932.

The total and differential leukocyte counts show no significant differences between the sexes at any age but display definite variations for the different age groups. The white cell count (chart 4) is higher for children aged from 4 to 7, with an average of 10,400 (10,365) and a range of from 6,000 to 15,000 per cubic millimeter, than it is for boys and girls from 8 to 18, with an average of 8,300 (8,342) and a range of from 4,500 to 13,500, or for adults, with an average of 7,400 (7,447) and a range of from 4,500 to 11,500. It should be noted that the range necessary to include 95 per cent of the values for adults is definitely wider than that usually given, 2 per cent of the results being less or greater than from 5,000 to 10,000 cells per cubic millimeter.

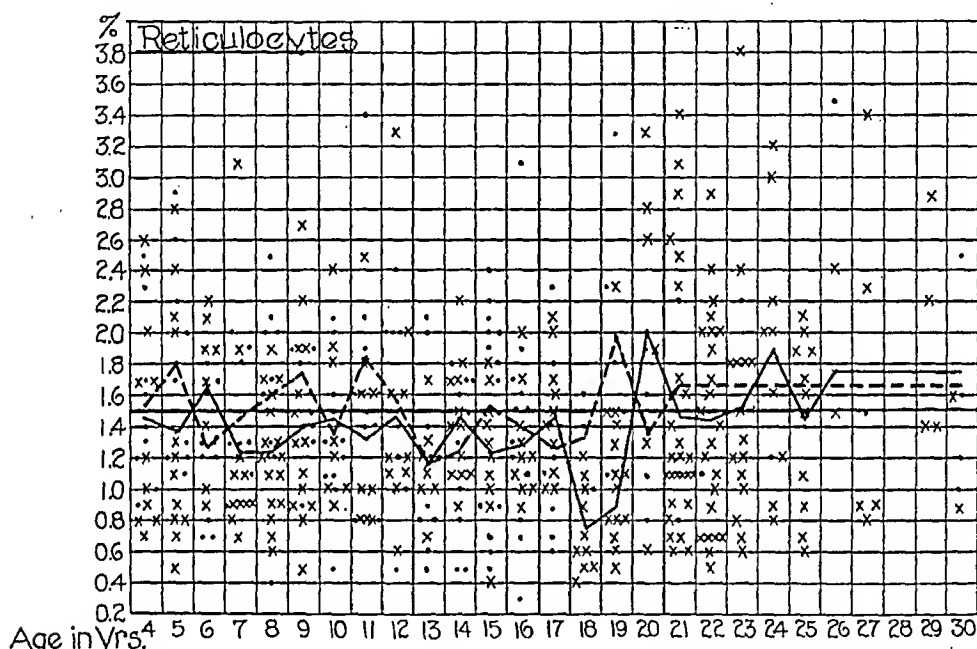


Chart 3.—Curves for the average values and the distribution of individual values for reticulocytes, expressed in percentages, for 275 males and for 173 females.

The number of segmented neutrophils (chart 4) is definitely lower for persons of all ages than the values usually given and shows a wider variation. Children aged from 4 to 14 have a lower average percentage, 38 (37.6), with a range of from 18 to 58 per cent, than adolescent boys and girls aged from 15 to 19 with an average of 48 (47.65) per cent and a range of from 25 to 75 per cent, or than adults, with an average of 54 (54.26) per cent and a range of from 33 to 78 per cent. This confirms a long held impression that the values usually given in textbooks are too high.

The separation of the staff cells (table 2) from the segmented neutrophils is not sufficient to explain the discrepancy, nor is the inclusion of disintegrating cells in the count, as the greatest value for the average total neutrophil count for adults that could be obtained by combining these results would be 58.5 per cent. It is of interest that

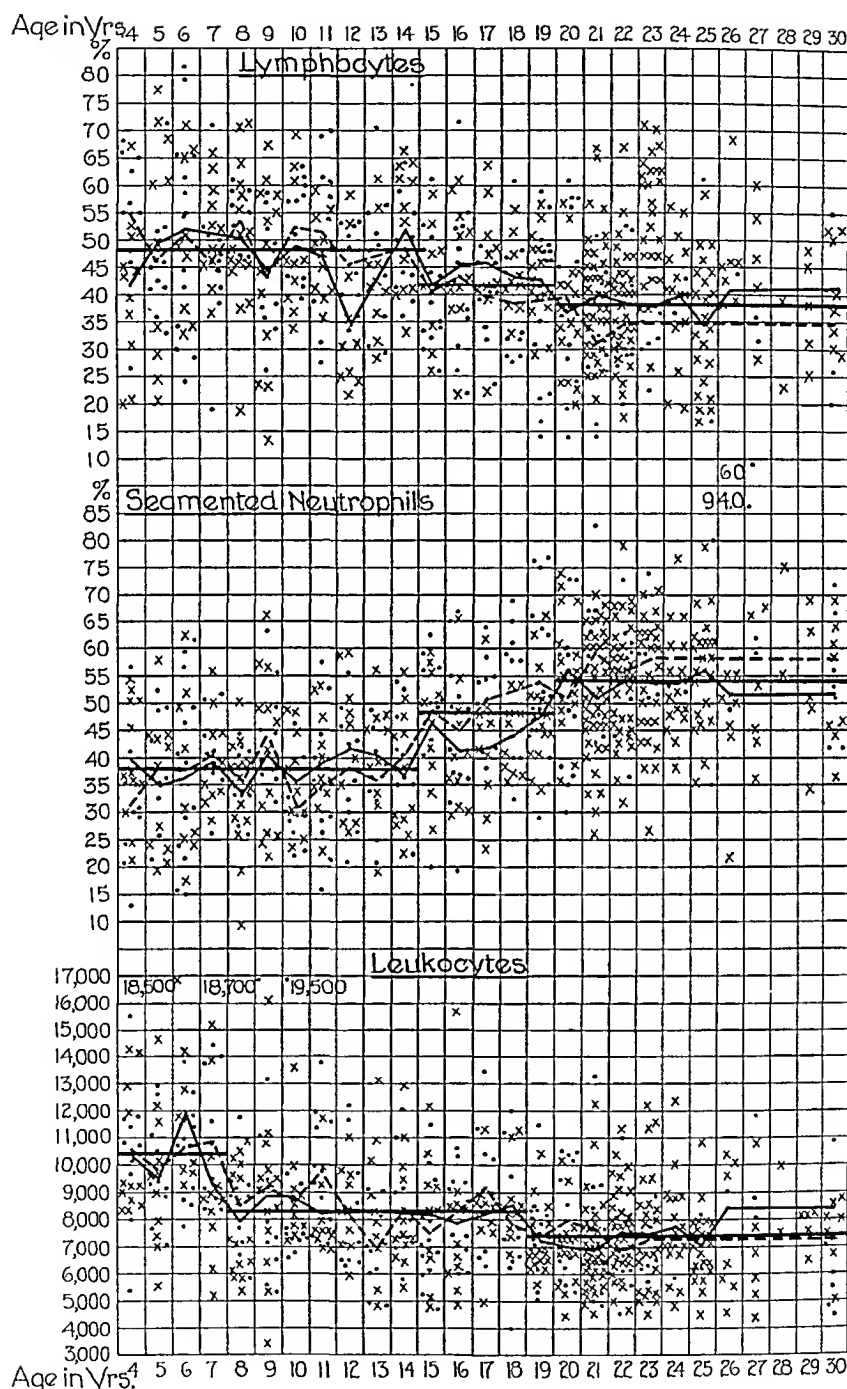


Chart 4.—Curves for the average values and the distribution of individual values for lymphocytes, segmented neutrophils and the total number of leukocytes for 365 males and 232 females. The values for the lymphocytes and segmented neutrophils are expressed in percentages; those for the total number of leukocytes, in thousands.

the number of staff cells is higher for children aged from 4 to 13, with an average of 3 (3.07) per cent and a range of from zero to 10 per cent, than for adults, with an average of 0.8 (0.78 per cent) and a range of from zero to 5 per cent.

The number of lymphocytes (chart 4), as might be expected, is in inverse ratio to that of the neutrophils but is much higher than the

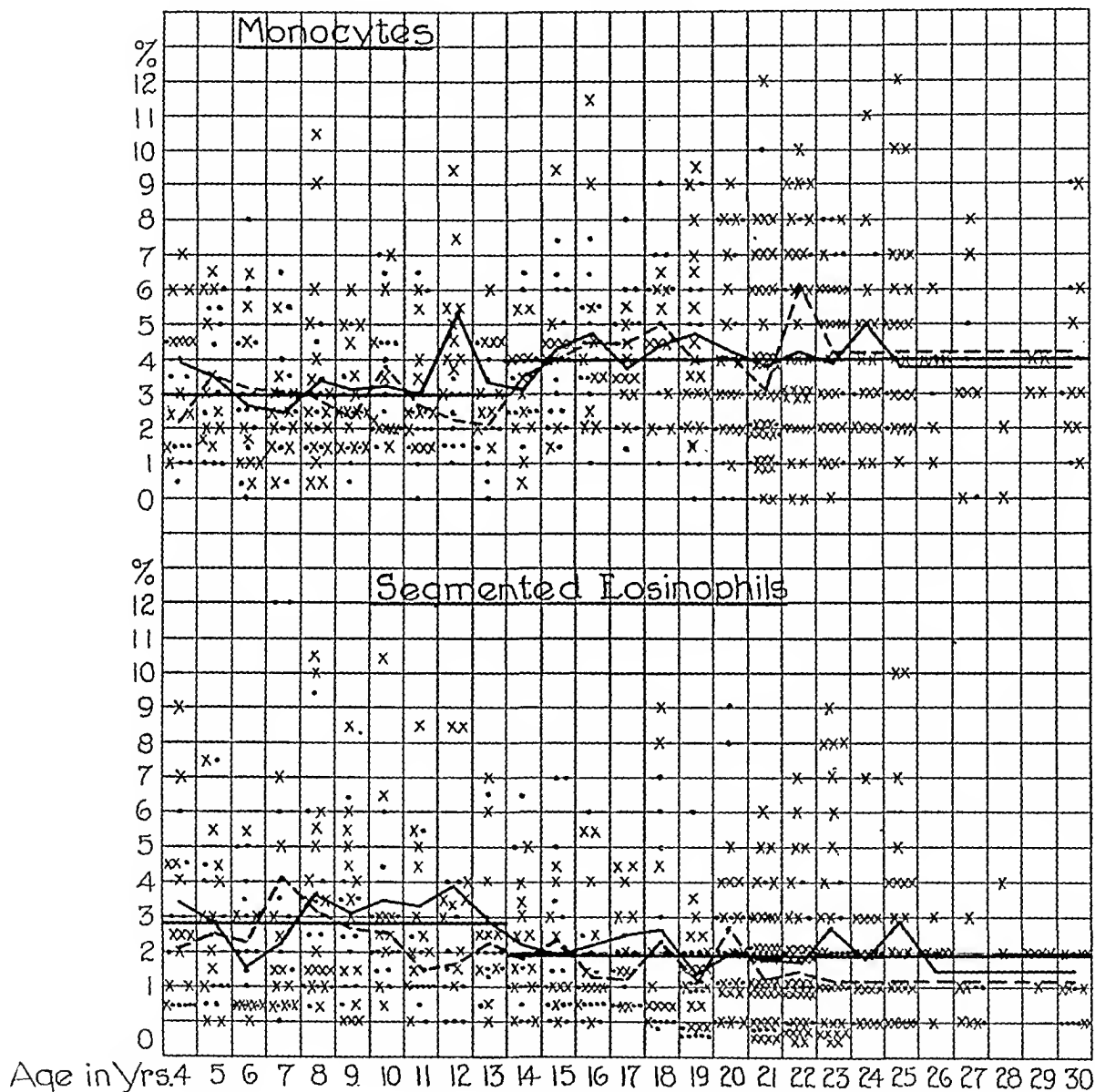


Chart 5.—Curves for the average values and the distribution of individual values for monocytes and segmented eosinophils, expressed in percentages, for 365 males and 232 females.

value usually employed. Children aged from 4 to 14 have an average count of 48 (48.21) per cent, with a range of from 21 to 71 per cent, and adolescent boys and girls from 15 to 19, an average of 42 (41.91) per cent and a range of from 22 to 62 per cent, while adults have an average of 38 (37.76) per cent and a range of from 18 to 65 per cent.

Age in yrs. 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

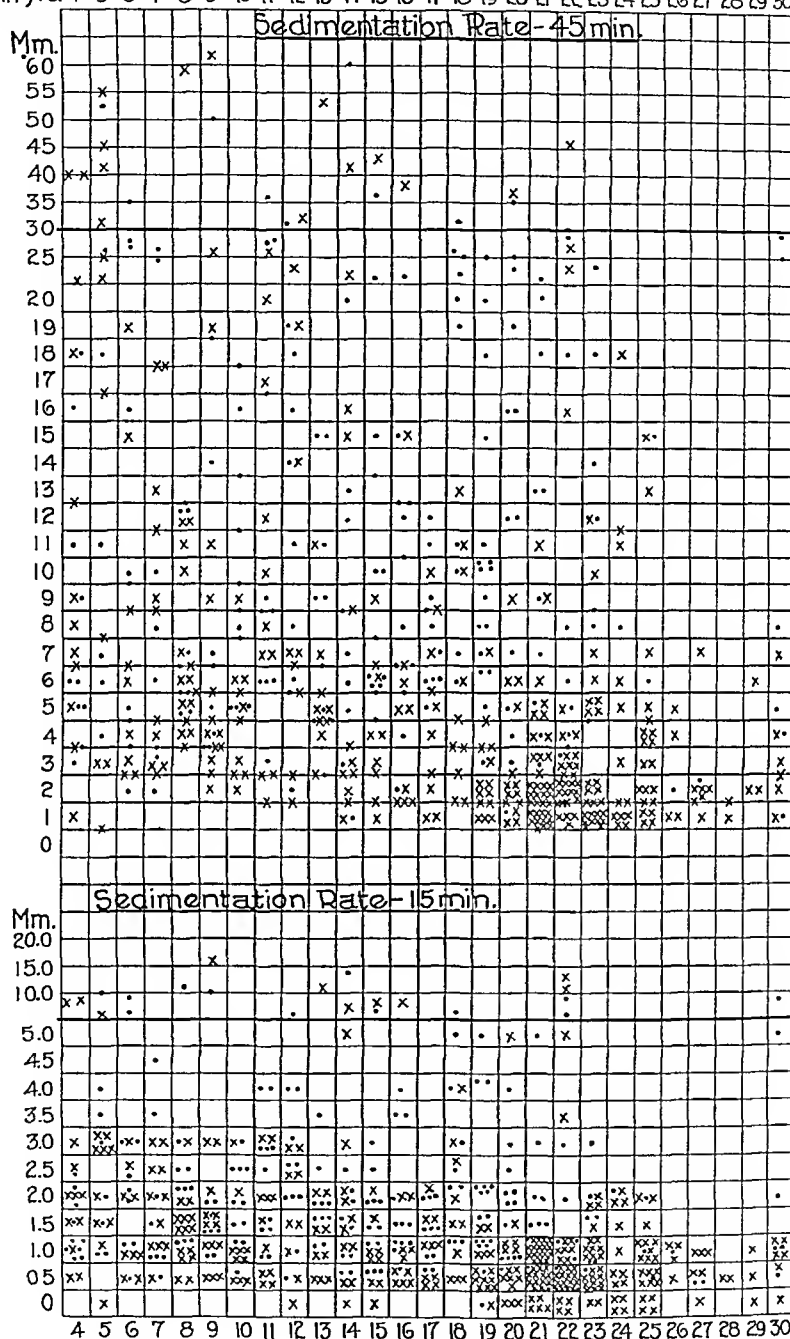


Chart 6.—Distribution of the individual values for the sedimentation rate, obtained for 340 males and 218 females at the end of forty-five minutes and of fifteen minutes, expressed in millimeters.

The number of monocytes and of eosinophils (chart 5) shows an inverse relationship, the percentage of monocytes being higher for adults and that of eosinophils higher for children. The number of monocytes averages 3 (3.08) per cent and ranges from 0.5 to 7 per cent for children aged from 4 to 13; for persons past the age of 14 the average is 4 (4.18) per cent and the range from 0 to 9 per cent. The number of segmented eosinophils averages 2.8 (2.79) per cent for children, with a range of from 0 to 8 per cent, and for persons past the age of 13 the number decreases to an average of 1.9 (1.9) per cent with a range of from zero to 6 per cent.

The number of basophils (table 2) shows no variation with age or sex, the average being 0.5 (0.52) per cent and the range from 0 to 2 per cent.

Disintegrating cells are often omitted in differential counts, but this introduces an error in the percentage of all the other cell types. The number of disintegrating cells furnishes an index of the rate of cell destruction. The increase in the number of disintegrating cells in cases of leukemia is often of diagnostic aid. These cells are more numerous in children, averaging 5 (4.89) per cent, with a range of from 0 to 10 per cent, than in adults, for whom the average is 3.5 (3.47) per cent and the range from 0 to 7 per cent.

In addition to the cell types listed in the table, Türk cells, plasma cells and eosinophil staff cells were found with sufficient frequency to justify one's regarding them as normal cells of the blood. An occasional promyelocyte or a large lymphocyte was found.

The sedimentation rates (chart 6) show a range of from 0 to 5 mm. in fifteen minutes and from 1 to 30 mm. in forty-five minutes. Undoubtedly, some high sedimentation rates are due to mild infections, such as chronic sinusitis or infected teeth, which are difficult to exclude by a routine physical examination. It is probable that the rate of 15 mm. in forty-five minutes, which includes 80 per cent of the results, is the upper limit of normal for persons entirely free from infection.

SUMMARY

Studies of the erythrocyte count, hemoglobin content, hemoglobin coefficient, cell volume, volume coefficient, color, volume and saturation indexes, reticulocyte count, total and differential leukocyte counts and sedimentation rate for more than 500 persons representing both sexes and all ages from 4 to over 30 years are presented.

The results of these studies are summarized in charts 1 to 6 and in table 2.

The normal hematologic standards given in table 2 should be used as a basis for interpretation until they are superseded by more extensive data of equal or greater accuracy.

RÔLE OF PRESSOR SUBSTANCES IN ARTERIAL HYPERTENSION

R. B. CAPPS, M.D.

E. B. FERRIS JR., M.D.

F. H. L. TAYLOR, PH.D.

AND

SOMA WEISS, M.D.

BOSTON

In the past, several investigators have postulated increased amounts of hormones of a pressor nature in the blood of patients with arterial hypertension. Others have suggested as a cause of hypertension the retention in the blood and tissues of metabolic products having a pressor action. One of us (Dr. Weiss¹) has recently discussed these various theories, and a critical analysis with references can be found in that paper. In recent years, interest in the relation of such substances to hypertension has been stimulated again, largely through the work of two groups of investigators in Germany. Lange and Felix,² in 1933, claimed to have found diminished amounts of a specific depressor substance in the blood and increased amounts in the urine of patients suffering from essential hypertension, and increased amounts in the blood and decreased amounts in the urine of patients with nephritic hypertension. They advanced the theory that essential hypertension is accompanied by a lowering of the renal threshold for this specific depressor substance, thus producing a lower concentration in the blood and thereby allowing the constrictor mechanism to overact. Because of the well recognized difficulties in isolating the various depressor materials present in blood and other tissues, and because of the complicated methods necessary for quantitative studies, the interpretation of these findings is difficult.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Weiss, Soma: The Etiology of Arterial Hypertension, *Ann. Int. Med.* **8**: 296, 1934.

2. Lange, Fritz: Der stoffliche Anteil an der Regulation des Kreislaufes und seine Bedeutung für die Hypertonie, *Klin. Wchnschr.* **12**:173, 1933. Felix, K.: Zur Chemie der stofflichen Kreislaufregulation, *ibid.* **12**:176, 1933.

In a series of studies Bohn and his associates,³ working in Volhard's Clinic, found markedly increased amounts of pressor material in both the blood and the urine of patients with "pale" hypertension (malignant and nephritic types) and noted its absence or its presence in only small amounts in normal subjects and in patients with "red" hypertension (essential and arteriosclerotic types). They claimed that by determining the amounts of pressor material in extracts of either the blood or the urine of hypertensive patients they could differentiate the pale from the red type. They thus confirmed Volhard's original postulation that pale hypertension is caused by increased amounts of circulating constrictor substances in the blood whereas red hypertension is the result of nervous and mechanical factors. Their methods of preparing extracts from the blood and urine are relatively simple, and their results appear to be clearcut and rather striking. The investigations of Marx and Hefke,⁴ based on a slightly different technic, were confirmatory of these findings. Anselmino and Hoffmann,⁵ using a method of dialysis, also separated active vasopressor material from blood. De Wesselow and Griffiths⁶ in England, and Page⁷ in this country, on the other hand, failed to confirm Bohn's findings with blood extracts. De Wesselow and Griffiths, using Bohn's methods, were unable to find any pressor material in the blood. Page found a pressor material in the blood; however, it was present as often in normal as in hypertensive subjects. Because of the importance of these findings in relation to the etiology and mechanism of hypertension, we have investigated certain aspects of this problem.

3. Bohn, H.: Untersuchungen zum Mechanismus des blassen Hochdrucks: I. Mitteilung. Gefäßverengernde Stoffe im Blute beim blassen Hochdruck, *Ztschr. f. klin. Med.* **119**:100, 1931; Zum Mechanismus des blassen Hochdrucks, vasoaktive und antidiuretische Stoffe im Blut, Liquor und Harn, Kreatin und Kreatinin im Blut und Harn, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **45**:182, 1933. Bohn, H., and Hahn, F.: Untersuchungen zum Mechanismus des blassen Hochdrucks: VI. Blutdrucksteigernde Stoffe im Harn, insbesondere beim blassen und roten Hochdruck, *Ztschr. f. klin. Med.* **123**:558, 1933.

4. Marx, H., and Hefke, K.: Untersuchungen zur Pathogenese der Hypertonie, *Klin. Wchnschr.* **12**:1318, 1933.

5. Anselmino, K. J., and Hoffmann, F.: Nachweis der antidiuretischen Komponente des Hypophysenhinterlappenhormons und einer blutdrucksteigernden Substanz in Blute bei Nephropathie und Eklampsie der Schwangeren, *Klin. Wchnschr.* **10**:1438, 1931.

6. de Wesselow, O. L. V. S., and Griffiths, W. J.: On the Question of Pressor Bodies in the Blood of Hypertensive Subjects, *Brit. J. Exper. Path.* **15**: 45, 1934.

7. Page, I. H.: Personal communication to the authors, *J. Exper. Med.* **61**: 67, 1935.

PLAN OF INVESTIGATION

The purpose of this investigation was to test the urine and blood of all types of hypertensive patients as well as of normal subjects for pressor substances by means of Bohn's technic. Our work has consisted chiefly in studies of urine extracts because in preliminary experiments we obtained no significant pressor effect from blood extracts prepared by various methods; furthermore, large quantities of urine could easily be obtained, and the substances to be studied could be more highly concentrated. We have limited ourselves to repeated observations on a small group of selected patients as it was felt that this would give the most significant information.

Extracts were prepared from the urine of each of twenty-five subjects, including seven with malignant hypertension, four with chronic nephritis and hypertension, six with essential hypertension and eight normal subjects.

The criteria adopted for the diagnosis of malignant hypertension included a marked elevation of both systolic and diastolic blood pressures, definite eyeground changes, such as hemorrhages, exudate and papilledema, and a relatively short duration of symptoms. The patients with essential hypertension showed only slight renal damage and had no retinal disturbances except for arteriosclerotic changes. Table 1 briefly summarizes these findings.

METHODS

In the preparation of the urine extracts Bohn's technic was followed in its original form as well as with modifications. Twenty-four hour amounts of urine were collected on ice, and the pressor material was adsorbed on a specially activated charcoal by shaking mechanically for five hours. The amount of charcoal used varied between 4 and 8 Gm. per liter of urine, depending on the amount of albumin present. The charcoal was then filtered off by suction and the dried charcoal extracted in a Soxhlet apparatus, first with acetone and finally with 95 per cent alcohol. In each case the extraction time was three hours. The extracts were evaporated to dryness *in vacuo* at temperatures not exceeding 37 C., and the residue of each extract was suspended or dissolved in 15 cc. of physiologic solution of sodium chloride. The extracts were then stored on ice until used.

Modifications of this technic resulted in no appreciable increase in pressor material. Since the alcohol extract was of necessity kept at a temperature of from 80 to 90 C. during extraction, cold extraction by continuous shaking for many hours was performed as an alternative method. Alcohol and acetone extraction of the charcoal in this way considerably diminished the activity of the extracts; prolonged extraction in the Soxhlet apparatus with both acetone and alcohol did not appreciably increase their activity.

In the preparation of blood extracts two technics were used: Fourteen of the blood extracts were prepared by Bohn's technic, which consisted in adding from 40 to 50 cc. of fresh blood to three times this volume of 95 per cent alcohol. The mixture was shaken and allowed to stand in the icebox for five hours. The precipitate was filtered off, and the filtrate was added to three times the original

blood volume of absolute alcohol and refiltered. The filtrate was then evaporated almost to dryness in vacuo and the residue dissolved or suspended in a volume of physiologic solution of sodium chloride equal to one half of the original volume of blood. The final extract was kept on ice until used.

In the preparation of five of the extracts Page's⁷ modification of Bohn's method was used. Freshly drawn citrated blood was centrifugated and the plasma pipetted into nine times its volume of absolute alcohol. The procedure to this point was completed within ten minutes after the venipuncture. The resulting mixture was allowed to stand on ice over night and was then rapidly filtered at a temperature not over 4 C. This removed the protein and most of the lipid material.

TABLE 1.—*Summary of Diagnoses and Clinical Findings in Patients Studied*

Case	Patient	Diagnosis	Age	Sex	Average Blood Pressure, Mm. Hg	Nonpro- tein Nitro- gen, Mg. per 100 Cc.	Renal Function	Fundi	Dura- tion of Symp- toms
1	R. S.	Malignant hypertension	46	M	200/140	36	Normal	Choking of disks; hemorrhages; narrowing of vessels	9 mos.
2	B. S.	Malignant hypertension	43	M	230/140	39	Slightly diminished	Choked disks; exu- date; hemorrhages	8 mos.
3	E. H.	Malignant hypertension	29	M	220/140	32	Normal	Narrowing of ves- sels; hemorrhages	3 yrs.
4	R. B.	Malignant hypertension	37	M	190/135	26	Normal	Narrowing of ves- sels; hemorrhages	2 wks.
5	S. L.	Chronic nephritis	41	M	260/150	44	Diminished	Choked disks; hemorrhages	2½ yrs.
6	P. S.	Malignant hypertension	56	M	230/155	32	Diminished	Choked disks; hemorrhages	1 yr.
7	B. D.	Chronic nephritis	52	F	240/130	44	Diminished	Hemorrhage; exudate	2 yrs.
8	C. C.	Chronic nephritis	21	M	175/124	49	Diminished	Narrowing of vessels	4 yrs.
9	J. A.	Malignant hypertension	49	F	240/130	32	Normal	Hemorrhage; exudate	1 yr.
10	M. K.	Chronic nephritis	37	F	190/122	37	Diminished	Narrowing of vessels	2 yrs.
11	W. H.	Malignant hypertension	47	M	240/160	38	Slightly diminished	Hemorrhage; exudate	6 mos.
12	J. L.	Essential hypertension	61	M	170/ 80	25	Slightly diminished	Arteriosclerotic retinitis	2 yrs.
13	R. C.	Essential hypertension	33	M	190/134	45	Normal	Narrowing of vessels	1 yr.
14	M. B.	Essential hypertension	39	F	220/110	36	Normal	Slight narrowing of vessels	1 yr.
15	A. T.	Essential hypertension	62	F	190/110	34	Normal	Nicking of veins	2 yrs.
16	J. W.	Essential hypertension	48	M	176/108	32	Normal	Normal	1 yr.
17	J. M.	Essential hypertension	64	M	170/ 90	32	Normal	Nicking of veins	1 yr.

Evaporation in vacuo to one half of the original volume of the plasma was carried out on the filtrate. The extract was then chilled to below 4 C. and any remaining lipid material precipitated and removed. The filtrate was kept on ice until injected.

About seventy cats were used in the studies with these extracts. Although sodium amytal (sodium salt of iso-amyl-ethyl barbituric acid) proved to be a satisfactory anesthetic, dial with ethyl carbamate (urethane)⁸ appeared to have

8. Dial with ethyl carbamate (urethane) is a solution prepared by the Ciba Company, Inc., 1 cc. containing diallylmalonylurea 0.1 Gm., ethyl carbamate (urethane) 0.4 Gm., mono-ethylurea, amount not stated, and distilled water.

a less depressant effect on the animals' vasomotor responses and was therefore used in the majority of the experiments. Both anesthetics were given intraperitoneally; the dose of sodium amytal was 0.05 Gm. per kilogram of body weight and that of the dial solution 0.7 cc. per kilogram of body weight. Ether, chloral and ethyl carbamate (urethane) were tried as anesthetics but did not prove as satisfactory as sodium amytal and dial.

The animals were regularly prepared by exposing both common carotid arteries and both vagus nerves and inserting a cannula into the trachea. The blood pressure was obtained from the femoral artery by means of a mercury manometer and was recorded on a smoked drum. Sodium citrate did not prove satisfactory as an anticoagulant; the wide variations in the blood pressure produced by the extracts caused the infusion of enough citrate into the blood stream to diminish the animals' pressor responses to a considerable degree. This was true even when concentrations as low as 5 per cent were used. Therefore, in most experiments a 0.5 per cent aqueous solution of heparin was employed. The arterial cannula, with a capacity of 5 cc., was filled with the heparin solution and the remainder of the system with isotonic sodium chloride. This method proved very satisfactory in preventing the formation of clots, and required only small amounts of heparin.

Urine extract was injected at a uniform rate into the femoral vein and washed into the circulation with 3 cc. of warm physiologic solution of sodium chloride. In order to standardize our results, 3 cc. of the extract, representing one fifth of the original twenty-four hour volume of urine, was used for each injection. A similar standard procedure was employed for the injection of blood extract. By testing a single extract on several animals, any variation in the pressor response between these animals was brought out and a true evaluation of the potency of a given extract could be made. Spontaneous variations in the response of each cat were likewise noted by frequent injections of the extract being tested.

The carotid sinus "pressor" reflex was elicited frequently by occlusion of both common carotid arteries in order to compare its effect with that of the extract and also in an attempt to test the animal's vasomotor sensitivity. Epinephrine in doses of 1 cc. of a 1:100,000 solution was used for similar purposes. In all cases the injection of extracts was preceded by the injection of a similar volume of saline solution in order to determine the blood pressure effect due to blood volume changes alone.

RESULTS

Types of Blood Pressure Responses Obtained.—The typical blood pressure response produced by the injection of urine extract consisted essentially in first a depressor and then a pressor effect. The depressor portion of the curve lasted from ten to thirty seconds and the pressor portion from three to thirty minutes. The magnitude of these two effects varied considerably in different experiments. A pure depressor curve was frequently obtained; a pure pressor curve more rarely. These various blood pressure reactions are similar to those described by Bohn and suggest, therefore, that we are dealing with the same pressor substance in the urine that he studied. Chart 1 shows the types of blood pressure curves observed by us.

Relationship of Pressor Substance to Hypertension.—Our results are summarized in table 2. We found no relationship between the magnitude of the pressor effect and hypertension of any type. In fact, we obtained on the whole more marked pressor responses with extracts of urines from normal subjects than with those of urines from patients having malignant and nephritic hypertension. The pressor effect was present to some degree, however, in about the same percentage of all groups of patients studied. We were unable to confirm Bohn's statement that pure pressor curves were obtained only in pale hypertension; in fact, all our pure pressor curves were obtained with extracts from the urines of normal patients.

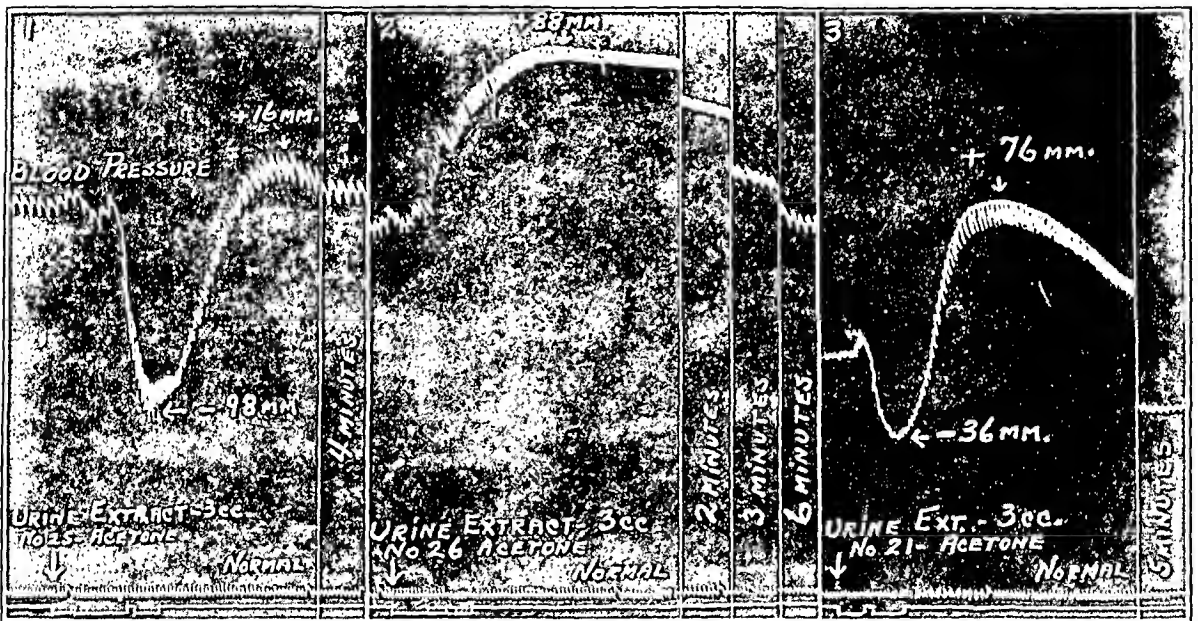


Chart 1.—Tracings obtained when extracts of urines from normal subjects were used, representing the various types of reactions obtained from all types of patients. These tracings correspond to Bohn's curve types 1, 3 and 2, respectively. Note that the pure pressor curve was obtained from a normal subject.

The factors influencing the type of blood pressure curve obtained with the urine extract of a given patient divide themselves into: variations related to the preparation and age of the extract, variations in the response of the test animal and daily variations in the excretion of the pressor material.

Variations in the Extract.—In his studies Bohn assumed that the acetone fraction removed only depressor material from the urine, and for this reason he tested only the alcohol fraction. We varied the time of extraction with acetone from a few minutes to twenty-four hours but were unable to substantiate Bohn's claim, and consequently have

tested both the acetone and the alcohol fraction from each urine studied. We have found no evidence that acetone selectively removes the depressor substances. In fact, on extracting with acetone for the same length of time as with alcohol, the acetone fraction produced in most cases more marked pressor and no greater depressor effect than did the alcohol fraction. By reversing the extraction process it was found that when the charcoal was extracted first with alcohol all the depressor and only half the pressor material was present in the alcohol, while 50 per cent of the pressor material remained to be extracted finally by the acetone. In the control experiment on the same sample of urine the acetone fraction contained all the pressor material and the final alcohol fraction only depressor material. This clearly demonstrates that under the conditions of our experiments, and in contradistinction to Bohn's findings, acetone is a better extractive for the pressor material than is alcohol.

TABLE 2.—*Summary of Pressor Responses Obtained from Extracts of Urines*

Condition of Patients from Whose Urines Extracts Were Obtained	Patients	Number Whose Urine Extracts Yielded Given Maximum Pressor Effect, Mm. Hg.					Urine Extracts Tested	Injec- tions of Extracts
		0-24	25-49	50-74	75-99	100+		
Normal.....	8	1	1	4	0	2	18	99
Essential hypertension..	6	3	2	0	0	1	8	30
Malignant hypertension	7	1	1	4	1	0	19	131
Chronic nephritis.....	4	1	1	2	0	0	8	39
Total.....	25	6	5	10	1	3	53	299

The age of the extracts after preparation, when these were kept in the icebox, appeared to have no influence on the type of response they produced in the cats. This was true for at least four weeks; in some cases the pressor effects then disappeared.

Variable Factors in the Cat.—The degree of both pressor and depressor responses in the same animal from repeated uniform doses of a single extract varied markedly for no discernible reason. Thus, in an experiment lasting several hours, an originally good pressor response was sometimes observed to disappear and then to reappear later, on successive test injections. This occurred in spite of attention to such details as the rate of injection, the temperature of the injected material and the temperature of the animal. The possibility that a prolonged action of the injected substance might account for variations in results was eliminated by always waiting at least ten minutes, or until the blood pressure had returned to its preinjection level, before testing another extract. A comparison of curves 4-A and 4-B in chart 2 demonstrates this change in the blood pressure response during a single experiment.

Bohn has stated that the initial blood pressure of the animal influences the pressor response to urine extract and that if it is too high it should be lowered by atropine, bleeding or the use of secondary butyl beta bromallyl barbituric acid sodium salts. We were unable to increase the pressor response of test animals to the urine extract by artificially lowering the blood pressure, either through the use of deeper anesthesia with dial, sodium amytal, chloral or ether, or through the use of atropine, bleeding or drugs having a depressor effect, such as amyl nitrite or acetylcholine. Although increased pressor effects were occasionally obtained by lowering the blood pressure through bleeding, this increase

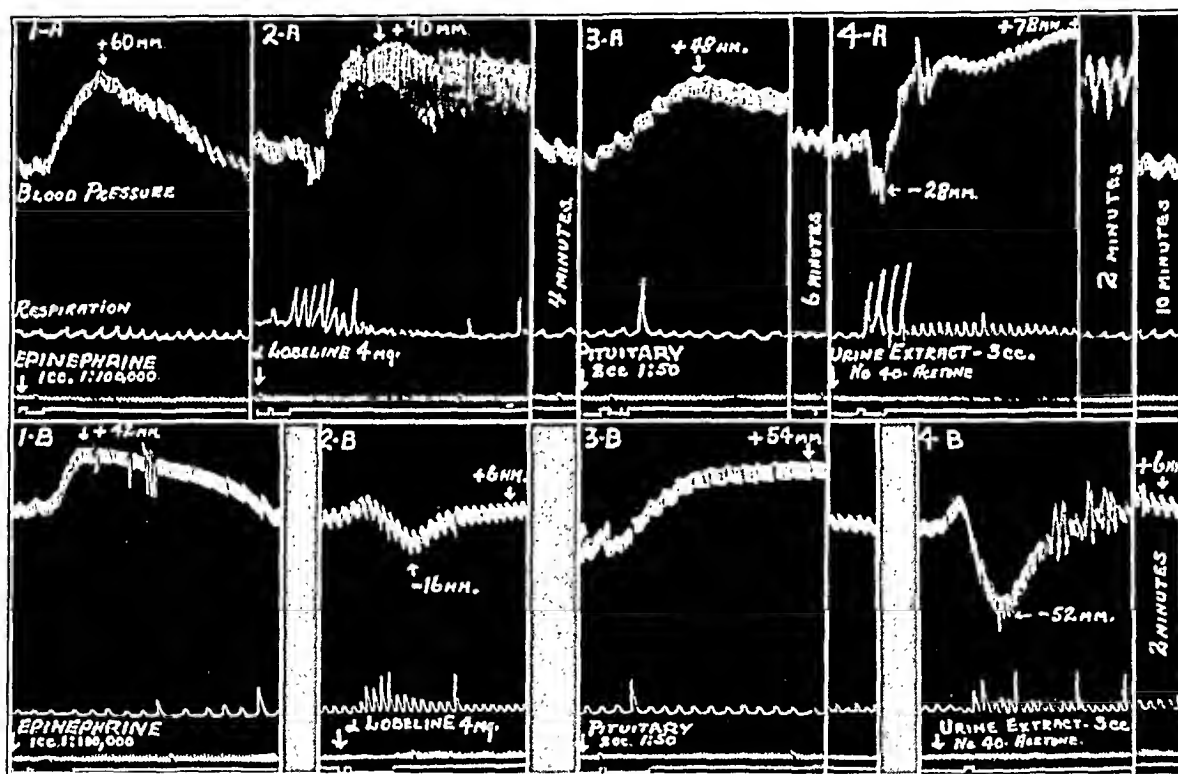


Chart 2.—The top row represents the blood pressure and respiratory response to the consecutive injection of epinephrine, alpha-lobeline, pituitary, and an extract of urine from a normal subject. The bottom row represents the response to these substances during a period when the pressor response to the urine extract had spontaneously disappeared. Note the similarity of the curve produced by lobeline to that produced by the urine extract during periods of both maximal and minimal response. Note also the lack of relationship between the pressor responses to epinephrine and pituitary and the response to the extract. This experiment also demonstrates the spontaneous change in the response of a test animal to a urine extract, which has been frequently encountered by us.

was proved to be largely due to the change in blood volume, as a rise in blood pressure approaching the difference of the pressor effects obtained could be produced by the injection of an equal volume of saline

solution. Increased pressor effects were, however, occasionally observed following spontaneous changes of the blood pressure to a lower level.

Comparison of the action of urine extracts from different patients would be greatly simplified if there existed a method for measuring the sensitivity of the test animal to the extract at a given time. Bohn thought that this sensitivity somewhat paralleled the action of epinephrine, and Page found a close relationship between the pressor effect of blood extracts and the carotid sinus pressor reflex. We have carried out both procedures, together with injection of the extracts, as a routine but have found no relationship whatsoever. In many cases the full pressor effect of epinephrine remained after that of the urine extract had disappeared (chart 2); furthermore, the epinephrine effect occasionally showed complete reversal during periods when maximal pressor effects were obtained from the extracts. Likewise, the pressor effect of the extract was found to be maximal during periods when the carotid sinus pressor reflex had disappeared. Both bilateral section of the vagus nerves and complete atropinization (1 mg. per kilogram of body weight) were carried out in some experiments, but neither of these procedures increased the pressor responses nor did they prevent the spontaneous variations in response to the extracts.

A comparison of the reactions of different animals to the same extract showed a satisfactory uniformity when the extract was injected under similar conditions.

Daily Variations in Excretion of Pressor Substance.—Extracts of the urine from a given patient, collected from day to day, generally gave the same type of blood pressure curve; however, marked variation in the daily excretion of the pressor substance was occasionally noted. This variation did not seem to be directly related to the volume of urine excreted; in fact, highly colored urines of small volumes appeared to produce the greatest pressor effects.

Nature of Pressor Substance Found in Urine.—Although the pressor material found in the urine bore no relationship to hypertension, its presence in such a large percentage of the urines tested led us to attempt to determine its nature and mode of action.

A depressor effect preceded the pressor curve in a large percentage of cases and suggested the possibility that the pressor portion of the curve was a nonspecific overcompensation on the part of the test animal to the initial depression of the blood pressure. This assumption was disproved by the fact that at times pure pressor effects were obtained and also by the fact that atropine abolished the initial depressor effect without materially changing the pressor response. The fact that atropine abolishes the depressor effect suggests that the depressor substances are in part choline or its derivatives.

Bohn and others have suggested that the pressor effect obtained from the urine is probably due to the presence of pituitary.⁹ We compared the response of the test animals to the urine extracts with the response to pituitary¹⁰ but found no relationship to exist between them. The pressor response to pituitary remained at a constant level or was even increased at times when the animal's response to the extract had entirely disappeared (chart 2). The dissimilarity of action between pituitary and the urinary pressor substance was brought out more conclusively in experiments which showed that the activity of pituitary is completely abolished by our method of extraction. In these experiments 4 cc. of pituitary was added to one half of a twenty-four hour specimen of urine and the remainder of the urine used as a control; both urine samples were carried through the usual method of extraction and concentrated so that 3 cc. of the final extract represented one fifth of a twenty-four hour volume of urine. Urines having a good pressor effect and others having only a depressor effect were extracted in this manner. In no case was there any difference between the blood pressure effect of the controls and that of the urine to which pituitary had been added. Had the pituitary remained active or been extracted, the 3 cc. of extract injected should have contained forty times the amount of pituitary necessary to raise the blood pressure of the animal 50 to 80 mm. of mercury. Likewise, repeated injections of epinephrine carried out in most experiments have demonstrated that there is no relationship between its action and that of the urine extract (chart 2). These observations clearly indicate that neither epinephrine nor pituitary is the pressor substance present in the urine. The shape of the pressor curves obtained from the urine extract, on the other hand, resembled in many respects those obtained from drugs with central vasomotor action. We have therefore compared the animal's response to the urine extract with that to alpha-lobeline. This substance has a central action and has been studied by Norris and Weiss¹¹ and others.¹²

9. Coester, C.: Untersuchungen zum Mechanismus des blossen Hochdrucks: IX. Pressorische und antidiuretische Stoffe im Harn beim blossen Hochdruck, *Ztschr. f. klin. Med.* **126**:593, 1934. Bohn,^{3b} Anselmino and Hoffmann.⁵

10. A double strength surgical pituitary.

11. Norris, V. H., and Weiss, S.: The Pharmacological and Therapeutic Properties of Alpha-Lobelin: A Comparison of Its Action on the Respiratory Center with That of Other Respiratory Stimulants, *J. Pharmacol. & Exper. Therap.* **31**:43, 1927.

12. Wieland, H.: Ueber die Alkaloide in Lobeliapflanzen, *Ber. d. deutsch. chem. Gesellsch.* **54**:1784, 1921. Edmunds, C. W.: On the Action of Lobelin, *Am. J. Physiol.* **11**:79, 1904.

The pressor action of alpha-lobeline was found to parallel closely the action of the extract; in fact, in experiments in which the two were injected repeatedly during changes in sensitivity of the cat, the pressor actions not only paralleled each other but the blood pressure curves showed strikingly similar changes in such details as the initial depressor effect, and delays in the pressor effect when the cat's sensitivity was rapidly diminishing.

Since the action of the urinary pressor substance closely parallels that of alpha-lobeline (a substance acting on the central nervous system) and shows no relationship to epinephrine and pituitary (substances having a peripheral action) it is suggested that the rise in blood pressure is due to central rather than to peripheral action. A comparison of the action of the extract with those drugs is shown in chart 2. In this experiment epinephrine, pituitary, lobeline and a single urine extract were repeatedly injected. It is seen that when the test animal had lost its pressor response to the extract the pressor action of lobeline likewise diminished, but that of epinephrine and of pituitary continued without change.

Although we have not compared the action of sympathin with that of the urinary pressor extract, it is obvious that the actions of the two substances are very dissimilar. The several types of sympathin are fairly unstable substances and have only a peripheral action¹³ whereas the pressor material is very stable and has a central action.

Effect of Blood Extracts.—In seventeen cases the method of Bohn, and in five cases the method of Page, was followed in extracting the blood. Extracts from the blood of both normal subjects and patients with malignant, essential and nephritic hypertension failed to produce any pressor effect other than that expected from the amount of fluid injected into the test animal.

COMMENT

In this study we have had some difficulty in reaching definite conclusions because of the many variable factors encountered. The determination of the pressor effect of a given extract required several observations on two or more test animals, and the injections had to be made at corresponding periods in each experiment. Also, the pressor effects from both the acetone and the alcohol fraction had to be considered together in estimating the total effect of a single extract.

The response of the test animal to a volume of saline solution equal in amount to that used in injection of the extracts was quite marked

13. Cannon, W. B.: Chemical Mediators of Autonomic Nerve Impulses, Science 78:43, 1933.

at times and had to be determined before estimating the pressor effects of the extracts. The types of pressor effects obtained from saline solution alone are shown in chart 3; elevations of the blood pressure as high as 30 mm. of mercury were frequently seen. In addition, numerous other factors previously mentioned had to be considered before the amount of pressor action of any extract could be estimated.

Because of the necessity of controlling these many variables, we feel that great caution should be used in arriving at significant conclusions in this type of problem. The failure to control properly such factors, in our opinion, is largely responsible for the conflicting results reported by various investigators concerning the relation of pressor substance to hypertension.

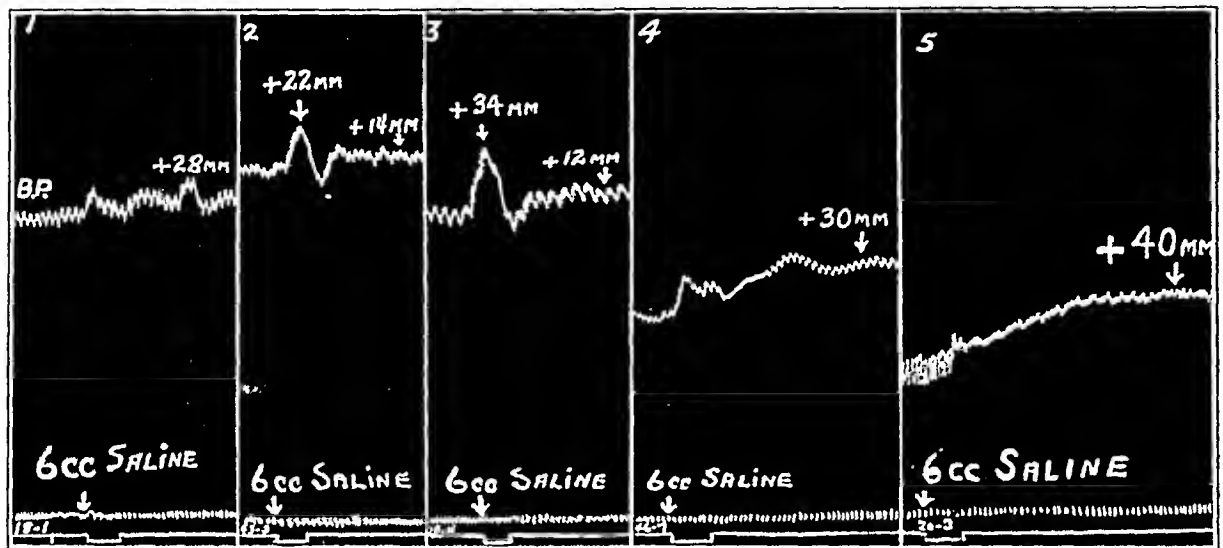


Chart 3.—Curves representing the pressor effects obtained from physiologic solution of sodium chloride. Curves 1, 2 and 3 are the types usually encountered, but elevations of from 30 to 40 mm. were frequently seen.

SUMMARY AND CONCLUSIONS

1. The pressor substance or substances in the urine of patients with hypertension of any type is not increased above the normal. The blood pressure response of test animals to extracts of urines from normal and hypertensive patients was essentially the same.

2. Removal of the depressor substances from the urine by acetone extraction did not prove satisfactory; on the whole, the acetone fraction contained more pressor material and less depressor material than did the alcohol fraction.

3. Although the exact nature of the pressor substance found in urine was not determined, we have presented experimental evidence

indicating that it is not epinephrine or pituitary, and that it is a rather stable water-soluble substance that acts centrally rather than on the peripheral nerve endings or on the vascular system.

4. The difference in the pressor effect of extracts from different patients, unless great, is not significant, because the methods of extracting and testing the pressor material are not sufficiently accurate.

THE RENAL THRESHOLD FOR DEXTROSE IN MAN

JAMES W. SHERRILL, M.D.

AND

EATON M. MacKAY, M.D.

LA JOLLA, CALIF.

By the renal threshold for dextrose is generally understood that concentration of sugar in the blood above which sugar appears in the urine. In man this phenomenon has long been of interest, especially in relation to diabetes. It has been frequently studied, but current opinion¹ is not in agreement as to the concept comprised in the term threshold for dextrose. The view of a fixed, unalterable concentration of dextrose in the plasma above which dextrose uniformly appears in the urine seems to be untenable. It is certain that by the ordinary methods of measurement there are many factors which cause the concentration to vary and that it not only is different in various persons but is not characteristic for a single subject. It is the purpose of the investigation reported here to examine some of the factors which it seemed might be largely responsible for a possibly apparent inconstancy of the renal threshold for dextrose.

THEORETICAL CONSIDERATIONS

In the light of our present knowledge of renal function as derived from direct experiments on the amphibian kidney² and the implications which they allow us to draw as to the mode of excretion of the urinary constituents by the mammalian kidney³ and even by the human kidney,⁴

From the Scripps Metabolic Clinic.

1. Himsworth, H. P.: The Relation of Glycosuria to Glycaemia and the Determination of the Renal Threshold for Glucose, *Biochem. J.* **25**:1128, 1931. Campbell, R. A.; Osgood, E. E., and Haskins, H. D.: Normal Renal-Threshold for Dextrose, *Arch. Int. Med.* **50**:952 (Dec.) 1932.

2. Richards, A. N.: Methods and Results of Direct Investigation of the Function of the Kidney, Baltimore, Williams & Wilkins Company, 1931. Oliver, J., and Shevsky, E.: A Comparison of the Manner of Excretion of Neutral Red and Phenol Red by the Frog's Kidney, *J. Exper. Med.* **50**:15, 1929; A Mechanism of Conservation in the Kidneys of the Winter Frog, *ibid.* **50**:601, 1929.

3. MacKay, E. M., and Oliver, J.: A Comparison of the Method of Excretion of Neutral Red and Phenol Red by the Mammalian Kidney, *J. Exper. Med.* **51**:161, 1930. Poulsson, L. T.: On the Mechanism of Sugar Elimination in Phlorrhizin Glycosuria, *J. Physiol.* **69**:411, 1930.

4. Chasis, H.; Jolliffe, N., and Smith, H. W.: The Action of Phlorrhizin on the Excretion of Glucose, Xylose, Sucrose, Creatinine and Urea by Man, *J. Clin. Investigation* **12**:1083, 1933.

the normal retention of dextrose in the blood by the kidney seems in all probability to be brought about by the almost complete reabsorption by the tubules of dextrose which is filtered from the plasma in the glomerular filtrate. That this reabsorption is normally not absolutely complete is indicated by the work of Eagle⁵ and of Van Slyke and Hawkins,⁶ who by the use of very sensitive modern methods found measurable quantities of reducing substances in normal urine. However, this is such an insignificant amount at most that for practical purposes the urine may be considered free from sugar. It is known that when the concentration of blood sugar rises to high levels, above the so-called threshold for dextrose, gross quantities of dextrose appear in the urine. It is our belief that there is sufficient evidence to allow one to consider this threshold for dextrose as the concentration of dextrose in the plasma at which the reabsorption of dextrose by the renal tubules from the glomerular filtrate is insufficient to prevent the excretion of an appreciable quantity of dextrose in the urine. From the theoretical aspect, one of the factors which seems likely to be foremost in determining this concentration is the degree of renal activity—not alone the number of functioning renal units but the activity of these or the volume of glomerular filtrate being formed in each individual unit. If only a relatively few glomerulotubular units were active, it is reasonable to suppose that a much higher concentration of dextrose in the plasma would be required to cause sugar to appear in the urine than if the kidneys were fully active. On the other hand, with all of the renal elements functioning, diuresis might so reduce the reabsorption of dextrose that a concentration of dextrose in the plasma considerably lower than usual might be reached before sugar-free urine would be formed. A suggestion that this is probably the case came from experiments on the threshold for sodium chloride, which are to be presented elsewhere. When rabbits were put on a salt-free diet and copious diuresis was established, a chloride-free urine was obtained when the average concentration of chloride in the plasma was 500 mg. per hundred cubic centimeters of sodium chloride. If extreme diuresis was induced by the administration of large amounts of urea and water, the urine again contained chloride when the concentrations of chloride in the plasma were much lower, even as low as 230 mg. per hundred cubic centimeters in one case, shortly after which the animal succumbed. On this basis the threshold for dextrose was investigated in man under conditions of full and constant renal activity.

5. Eagle, H. S.: On the Nature of the Urine Sugars, *J. Biol. Chem.* **71**:481, 1927.

6. Van Slyke, D. D., and Hawkins, J. A.: *J. Biol. Chem.* **83**:51, 1929.

Various observers, beginning with Frank,⁷ have noted that the renal threshold determined on the basis of a descending curve of sugar concentration in the blood may be entirely different from the threshold derived from an ascending curve. It is the usual conclusion⁸ that the threshold level is much lower during a descending curve. The reason for this discrepancy probably rests in the dead space of the kidney and ureter. Hinsworth^{1a} has considered the influence of this dead space, but not for the same reason. The urine from the bladder, as collected, has actually been formed from two to even sixty minutes before it reaches the bladder, depending on the rate of the secretion of urine—the lower the rate the greater the difference in time. With volumes of urine of 20 cc. or less per hour, the renal threshold determined on the basis of a descending curve of sugar concentration in the blood drawn at the middle of an apparent period of urine secretion would be much too low. The only way to remove this factor entirely would be to determine the renal threshold for dextrose during the continuous intravenous injection of dextrose, only those periods being selected in which the concentration of blood sugar during the fore-periods and after-periods was approximately the same. Obviously this method is impracticable for any series of observations. The error may be greatly reduced by insuring high volumes of urine and thus reducing the time interval represented by the urine in the dead space.

Many investigators are accustomed to thinking of the concentration of dextrose in the urine in determining the renal threshold. This figure is, however, determined not only by the excretion of dextrose but by the volume of urine. With a qualitative clinical test (Benedict's), such as is frequently made, a volume of urine of 30 cc. per hour will not give a positive reaction if it contains 200 mg. of sugar. With one-half this volume the same amount of sugar will give a strong reducing action. The only reasonable method of expressing the dextrose in the urine is in the rate of dextrose excreted per unit of time.⁹

The blood which forms the urine is arterial. There is quite a discrepancy between the concentration of dextrose in arterial blood and that in venous blood,¹⁰ and the former is the one from which determinations of the level of the renal threshold for dextrose should be made. Technically, the difficulty of obtaining arterial blood may be overcome by the use of capillary blood, which is practically arterial so far as the sugar content is concerned.¹⁰ The ideal condition would be to use

7. Frank: *Arch. exper. Path. u. Pharmacol.* **72**:387, 1913.

8. Goto, K., and Nobuzo, K.: *Studies on Renal Threshold for Glucose*, *Arch. Int. Med.* **27**:224 (Feb.) 1921.

9. Hawkins, J. A.; MacKay, E. M., and Van Slyke, D. D.: *Glucose Excretion in Bright's Disease*, *J. Clin. Investigation* **8**:107, 1929.

10. Foster, G. L.: *Some Comparisons of Blood Sugar Concentrations in Venous Blood and in Finger Blood*, *J. Biol. Chem.* **55**:291, 1923.

arterial plasma, but this is naturally not practicable. Then it is generally customary to use whole blood rather than plasma for analyses of blood sugar.

It must be remembered that not all of the reducing substances in either the urine or the blood are dextrose. In measuring the renal threshold for dextrose, only the fermentable reducing substances in both the blood and the urine should be determined. Otherwise, one must deal with a variable and unknown quantity of nondextrose reducing substances included in their figures for dextrose.

So far as possible, certain refinements have been introduced into the method of determining the threshold for dextrose which from the theoretical aspects discussed may determine the usual inconstancy of this figure.

EXPERIMENTAL PROCEDURE

Adequate volumes of urine and full renal activity were attained by the administration of urea and large quantities of water under conditions¹¹ which are known to yield this result. The patient was kept without food for twelve hours before and for the duration of the period of observation, so that the degree of renal activity might remain constant.¹²

Dextrose when given by mouth with a moderate quantity of fluid has long been known¹³ to produce oliguria and in some instances complete suppression of urine. Allen¹³ has shown that it is only in the severely diabetic organism that dextrose administered in any other way than intravenously produces polyuria rather than an antidiuretic effect. The stimulation of renal activity afforded by the large amounts of urea and water might be expected to overcome this oliguria, but even when the depressed volumes of urine are still reasonably high we have found a marked decrease in the degree of renal activity as measured by the urine-blood urea relationship following the ingestion of 100 Gm. or more of dextrose under these conditions. Since we desired to avoid this and as many of the subjects did not have severe diabetes, dextrose was administered intravenously. The procedure for each experiment was essentially as follows:

The subjects were given no food or fluids for a period of twelve hours preceding the determinations. Each subject was given approximately 0.25 Gm. of urea and 20 cc. of water per kilogram by mouth at 6 a. m. Ten cubic centimeters

11. Addis, T.: The Ratio Between the Urea Content of the Urine and of the Blood After the Administration of Large Quantities of Urea, *J. Urol.* **1**:263, 1917.

12. Addis, T., and Drury, D. R.: The Effect of Changes in Blood Urea Concentration on the Rate of Urea Excretion, *J. Biol. Chem.* **55**:105, 1923.

13. Allen, F. M.: Studies Concerning Glycosuria and Diabetes, Cambridge, Mass., Harvard University Press, 1913, chap. 6. Sherrill, J. W., and John, H. J.: The Influence of Glucose Ingestion on Diuresis and Blood Composition in Non-Diabetic or Diabetic Persons, *J. Metab. Research* **1**:109, 1922.

of water per kilogram of body weight was given each hour thereafter until the observations were ended. By 9 a. m. full renal activity with good diuresis had been established, and from 25 to 50 Gm. of dextrose in 50 per cent solution was given intravenously through one of the superficial veins of the arm. All intervals on the chart were measured from this point. The patient at once emptied his bladder completely, and specimens of urine were saved after this. They were collected at 30, 60, 90, 120, 150, 180, 210 and 240 minutes. Specimens of blood were taken at the middle of each period of urine collection, that is, at 15, 45, 75, 105, 135, 165, 195 and 225 minutes after the ingestion of dextrose. The subject remained in bed throughout the test and received no other fluid, food or medication during this period.

The determinations of the blood sugar were made by the micromodification of the Shaffer-Hartman method suggested by Somogyi.¹⁴ By the use of Somogyi's zinc sulphate reagents¹⁵ for removing the blood proteins, the nonfermentable reducing substances were removed from the filtrate at the same time. Samples of blood of 0.2 cc. each were collected in a long, accurate 15 cm. calibrated capillary pipet and washed out with the diluting fluid. The blood was obtained by a

TABLE 1.—Results of a Typical Experiment on Determination of the Renal Threshold for Dextrose

Urine Collected		Dextrose Excreted, Mg. per Hr.	Blood Dextrose, Mg. per 100 Ce.
Time, Min.	Volume Rate, Cc. per Hr.		
30	920	2,520	280
30	330	465	219
30	430	196	184
30	600	18	149
30	490	9	107
30	550	0	68
Dextrose threshold.....			128 mg.

clean deep prick of the finger with a sharp lancet after the hand had been held for some minutes in hot water.

The fermentable reducing substances of the urine were determined by a modification of the Shaffer-Hartman method,¹⁶ yeast fermentation being used for the removal of nonsugar substances. With our dilute urines the dilution described by the authors was unnecessary.

RESULTS

With the very rigid methods that have been described as ideal for determining the renal threshold for dextrose, observations have been made on ten persons with diabetes and eleven patients without known abnormalities in their carbohydrate metabolism and apparently with normal kidneys. A typical experiment is presented in table 1. The observations from each experiment necessary for determining the threshold form table 2. We have assumed for present purposes that a

14. Shaffer, P. A., and Somogyi, M.: Copper-Iodometric Reagents for Sugar Determination, *J. Biol. Chem.* **100**:695, 1933.

15. Somogyi, M.: A Method for Preparation of Blood Filtrates for the Determination of Sugar, *J. Biol. Chem.* **86**:655, 1930.

16. Harding, V. J., and Van Nostrand, F. H.: Variations in Blood and Urinary Sugar After the Ingestion of Galactose, *J. Biol. Chem.* **85**:765, 1930.

TABLE 2.—Observations from Each Experiment Necessary to Determine the Renal Threshold for Dextrose

No.	Period, Min.	Urine Volume, Cc. per Hr.	Urine Dextrose, Mg. per Hr.	Blood Dextrose, Mg. per 100 Cc.	No.	Period, Min.	Urine Volume, Cc. per Hr.	Urine Dextrose, Mg. per Hr.	Blood Dextrose, Mg. per 100 Cc.
N. D. 1	30	530	495	180	D 1	30	140	81	210
	30	530	0	134		30	160	30	173
						30	70	9	158
2	30	280	200	190	2	30	230	510	194
	30	410	11	152		30	640	4	130
	30	470	0	140	3	30	690	1,692	211
						30	700	300	197
3	30	750	67	154		30	610	12	163
	30	500	0	121		30	580	0	160
					4	60	200	32	179
4	30	430	196	184		30	660	7	158
	30	600	18	149		30	610	0	149
	30	490	9	107	5a	30	510	41	162
	30	550	0	68		30	430	0	150
5	30	470	117	171	5b	30	280	1,316	193
	30	450	41	162		30	530	22	157
	30	520	0	94		30	610	0	152
					5c	30	470	301	271
6	30	480	170	168		30	520	62	163
	30	520	8	64		30	410	0	133
	30	660	0	56	6a	30	110	10	182
						30	420	5	124
7	30	300	378	112	6b	30	630	196	178
	30	340	7	99		30	640	52	150
	30	390	0	86		30	580	4	134
					6c	30	170	46	163
8	30	400	200	196		30	230	11	142
	30	620	12	104		30	640	4	133
	30	610	0	93	7	45	390	68	157
						30	320	0	135
9	30	520	37	132	8	30	230	560	193
	30	450	15	104		30	160	71	160
	30	710	0	96		30	240	3	132
					9	30	270	18	151
						30	190	0	111
10	30	390	776	109	10	30	720	1,210	173
	30	320	12	95		30	680	68	146
	30	300	0	71		30	530	0	98

TABLE 3.—Renal Threshold for Dextrose in a Group of Persons with Diabetes and a Group Without Diabetes

Case	Sex	Age, Years	Dextrose Threshold	Comment
Persons Without Diabetes				
1	F	32	157	Bronchiectasis
2	M	50	146	Mild hypertension
3	F	55	138	Normal
4	F	14	128	Mild obesity
5	F	53	128	Thyroidal obesity
6	F	50	116	Hypertension
7	F	71	106	Hypertension
8	F	43	101	Obesity
9	F	55	100	Past undernutrition
10	F	55	83	Asthma
11	M	61	78	Normal
Diabetic Patients				
1	F	70	165	Severe diabetes
2	M	67	162	Severe diabetes; 10 years' duration
3	F	59	161	Moderate severity; 2 years' duration
4	M	67	160	Mild diabetes; 2 months' duration
5a	F	51	156	Severe diabetes
5b	F	51	154	
5c	F	51	148	
6a	M	14	153	Mild diabetes
6b	M	16	142	
6c	M	16	138	
7	F	55	146	Mild type
8	F	74	146	Severe diabetes; 8 years' duration
9	F	22	131	Moderate severity; 2 years' duration
10	F	58	122	Trivial diabetes for 1 year

urine containing 10 mg. or less of dextrose per hour is sugar-free. The analytic methods in our hands make the measurement of this amount questionable. We have chosen as the renal threshold for dextrose the average of the midperiod values for blood dextrose for the last period in which sugar was found in the urine and for the first period in which there was no sugar. Certain pertinent data and the renal thresholds for dextrose are presented in table 3.

With the particular groups which were examined the renal threshold for dextrose was on the average definitely higher in persons with diabetes than in those who did not have diabetes. The average for the former group was 149 mg. per hundred cubic centimeters in comparison with 128 mg. for the latter group. There was a large degree of variability in both groups. In the two persons (D5 and D6) for whom repeated determinations were made a rather good degree of constancy was found.

CONCLUSIONS

These experiments and our consideration of the factors involved in the determination of the renal threshold for dextrose lead us to the conclusion that the threshold as a "normal figure" is a misnomer. That a given subject has his own particular level above which sugar appears in the urine is probable, provided the conditions are the same each time. Under ordinary circumstances the figure found simply represents the situation as it exists at that particular moment. A normal average for the renal threshold should never be given, for it may be misleading.

For practical purposes the renal threshold for dextrose is of clinical interest only when dextrose is detected in the urine, for this indicates either hyperglycemia or a so-called "renal diabetes." In the absence of sugar in the urine qualitatively the renal threshold has no place.

EFFECT OF LOW CALORIC DIETS AND RESULTANT LOSS IN WEIGHT ON PLASMA CHOLESTEROL IN THE OBESE

CHARLES A. POINDEXTER, M.D.*

AND

MAURICE BRUGER, M.D.†

NEW YORK

In a previous communication¹ we showed that in obese subjects in whom evidence of metabolic disorders (diabetes mellitus, including the prediabetic state, essential hypertension and arteriosclerosis) and arthritic disturbances (osteo-arthritis) was lacking the cholesterol content of the plasma was usually at a normal level. The advent of these degenerative diseases in the obese was generally accompanied by a rise in the plasma cholesterol.

The second phase of the problem, namely, a study of the variations in the blood cholesterol in obese subjects undergoing reduction of weight on a low caloric diet, is now reported. We wished to determine whether loss in weight while on a low caloric diet exerted any influence on the normal level of the plasma cholesterol in subjects with uncomplicated obesity and, again, whether the elevated plasma cholesterol in obese persons showing evidence of degenerative disease could be reduced by a similar diet.

MATERIAL AND METHODS

Thirty subjects, chosen at random from our original group of ninety-four, were placed on a low caloric diet, and the body weight and plasma cholesterol were determined at more or less regular intervals for from six to sixty weeks. Table 1 indicates the cases studied (the numbers of the cases conform with those employed in our previous paper¹ and represent the same subjects), the original weight, the percentage overweight, the length of the study, the number of determinations of cholesterol and the loss in weight. The average patient weighed 207 pounds (94.1 Kg.), was 49.6 per cent overweight, and lost 20 pounds (9.1 Kg.) during twenty-two weeks of observation; nine determinations of cholesterol were made serially.

* Harriet Weil Fellow in Medicine.

† Oliver Rea Fellow in Medicine.

Aided by a grant from the Josiah Macy Jr. Foundation.

From the Department of Medicine, the New York Post-Graduate Medical School and Hospital.

1. Bruger, M., and Poindexter, C. A.: Relation of the Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases (Diabetes Mellitus, Essential Hypertension, Osteo-Arthritis and Arteriosclerosis), *Arch. Int. Med.* **53**:423 (Feb.) 1934.

The subjects were ambulatory and were followed in the clinic for obese patients of the New York Post-Graduate Hospital. Without exception, all venipunctures were carried out in the morning, in most cases after the patient had partaken of the prescribed breakfast.

The cholesterol content of the plasma was determined by Sackett's modification of the Bloor method,² with the temperature control procedure employed in this laboratory for colorimetric estimation.³

TABLE 1.—*Original Weight, Percentage Overweight, Length of Study, Number of Determinations of Plasma Cholesterol and Loss in Weight on a Low Caloric Diet in Fourteen Cases of Uncomplicated Obesity and in Sixteen Cases of Obesity Complicated by Metabolic, Arthritic or Endocrine Disturbances, Which Form the Basis for the Present Study*

Case	Class	Original Weight, Pounds	Percentage Overweight	Length of Study, Weeks	Number of Cholesterol Determinations	Loss of Weight, Pounds
2	Uncomplicated.....	164	23.3	10	5	8
10	Uncomplicated.....	172	27.4	20	16	22
14	Uncomplicated.....	194	32.9	7	4	9
21	Uncomplicated.....	211	40.6	6	4	13
22	Uncomplicated.....	183	43.0	25	4	27
23	Uncomplicated.....	172	43.3	10	6	16
26	Uncomplicated.....	265	46.4	23	5	23
27	Uncomplicated.....	197	48.1	20	11	30
32	Uncomplicated.....	231	56.0	13	5	10
37	Uncomplicated.....	216	58.8	41	9	28
38	Uncomplicated.....	209	59.5	23	6	13
41	Uncomplicated.....	193	60.8	29	8	35
49	Uncomplicated.....	224	80.7	12	3	16
53	Uncomplicated.....	292	107.0	10	7	33
56	Metabolic.....	192	23.0	60	24	23
59	Metabolic.....	187	29.9	11	6	12
60	Metabolic.....	182	30.9	22	10	12
62	Metabolic.....	194	34.7	13	4	14
64	Metabolic.....	168	35.5	9	4	5
66	Metabolic.....	168	37.7	53	39	16
71	Metabolic.....	188	46.7	16	7	12
73	Metabolic.....	233	64.1	17	5	12
76	Metabolic.....	225	70.5	32	4	16
77	Metabolic.....	298	122.3	33	9	42
80	Arthritis.....	175	22.4	9	5	10
83	Arthritis.....	173	31.1	13	6	3
84	Arthritis.....	197	36.8	50	17	37
85	Arthritis.....	187	39.6	13	5	22
92	Endocrine.....	227	65.7	22	10	17
93	Endocrine.....	280	65.7	27	11	49
Average.....		207	49.6	22	9	20

RESULTS

Table 2 indicates the results obtained in fourteen cases of uncomplicated obesity. It is significant from this protocol that reduction in weight is not accompanied by any uniform trend of the plasma cholesterol content; in general, marked loss in weight in the obese is usually associated with no alteration in the cholesterol content of the plasma (cases 23, 26, 27, 37, 41 and 53).

2. Sackett, G. E.: Modification of Bloor's Method for Determination of Cholesterol in Whole Blood or Blood Serum, *J. Biol. Chem.* **64**:203, 1925.

3. Mirsky, I. A., and Bruger, M.: A Note on the Liebermann-Burchard Color Reaction for Cholesterol, *J. Lab. & Clin. Med.* **18**:304, 1932.

Two cases were exceptional. In case 10 there was initial hypercholesteremia. With loss in weight on a low caloric diet, there was a suggestive fall in the amount of plasma cholesterol. It is difficult to explain this result unless it is assumed that the patient may have shown

TABLE 2.—*Effect of a Low Caloric Diet and Resultant Loss in Weight on the Plasma Cholesterol in Fourteen Cases of Uncomplicated Obesity**

Time, Weeks	Choles-terol	Weight	Diet	Time, Weeks	Choles-terol	Weight	Diet	Time, Weeks	Choles-terol	Weight	Diet
Case 2				Case 23				Case 37			
0	229	164		0	179	172		0	183	216	
3	213	161	1	2	172	171	None	2	136	208	5
5	204	157	2	4	185	165	4	4	175	199	1
8	248	156	1	6	174	164	4	6	155	195	1
10	194	156	2	8	201	161	4	7	167	193	1
				10	188	156	4	20	172	187	1
Case 10								22	156	183	1
0	301	174						24	170	180	1
1	324	170	1					41	176	188	1†
3	352	170	3	Case 26				Case 38			
5	347	165	3	0	147	265		0	206	209	
7	278	162	3	13	181	243	4	1	214	207	5†
9	259	159	3	16	199	242	4	8	216	203	5†
12	263	157	3	19	161	240	4	10	180	200	5†
14	295	155	3	23	167	237	4	13	183	198	5†
16	274	151	3					23	152	196	5†
18	295	151	4					Case 41			
20	276	150	4					0	194	198	
Case 14				0	192	197		4	204	179	5
0	202	194		2	162	193	5	6	184	177	5
3	232	192	5	4	175	187	1	8	192	173	5
5	226	189	5	6	142	184	1	14	230	163	5
7	192	185	5	8	176	180	1	17	195	160	1
				10	149	179	1	21	227	159	1
Case 21				12	169	174	1	29	226	158	1
0	149	211		14	149	170	1				
2	143	206	1	16	221	168	6	Case 49			
4	121	200	1	19	165	167	5	0	214	224	
6	175	198	1	20	172	167	6	3	179	220	1X
								12	248	208	1Y
Case 22				Case 32				Case 53			
0	216	183		0	216	231		0	168	294	
20	233	158	1	2	235	231	4	1	192	284	None
22	245	157	1	4	180	224	4	3	206	278	5
25	260	156	1	8	223	222	1	5	173	270	5
				13	206	221	1†	7	173	265	5
								10	175	254	5

* In tables 2 and 3 the cholesterol is expressed in milligrams per hundred cubic centimeters of plasma and the weight in pounds. The diets employed were as follows:

Diet	Carbo-hydrate	Protein	Fat	Calories	Diet	Carbo-hydrate	Protein	Fat	Calories
1	35	70	20	600	5	65	80	40	940
2	45	75	30	750	6	80	80	40	1,000
3	65	79	20	756	7	100	96	56	1,298
4	85	80	25	885					

† This patient was taking food in excess of the prescribed diet.

X indicates 1 grain of thyroid daily; Y, erysipelas; Z, cerebral thrombosis.

impairment of sugar tolerance (so-called prediabetic state), which would account for the initial elevated value for plasma cholesterol, and that the decrease in the cholesterol content was associated with an improvement in carbohydrate tolerance consequent to the ingestion of a low caloric diet and reduction in weight. In case 38 also there was a signifi-

cant fall in the plasma cholesterol content following loss in weight. The subject, however, had rheumatic cardiac disease with mitral stenosis and showed signs of increasing décompensation, which probably accounts for the gradual diminution of the amount of blood cholesterol (a low blood cholesterol content in association with cardiac decompensation is not an uncommon finding).

Table 3 indicates the results obtained in sixteen cases of obesity complicated by metabolic, arthritic and endocrine disturbances. In general, the findings are similar to those just discussed for the uncomplicated group; namely, moderate to marked loss in weight, provided no obvious change has taken place in the complicating disease, is usually associated with no alteration in the cholesterol content of the plasma (cases 59, 60, 62, 71, 76, 77, 84, 92 and 93).

The diminishing blood cholesterol content in cases 56 and 66 accompanying loss in weight can probably be accounted for by change in the clinical status of the patients. In case 56 the patient showed increasing cardiac embarrassment as result of long-standing hypertension; definite signs of cerebral thrombosis became evident forty-six weeks after the study was begun. In case 66 the patient had diabetes and required 8 units of insulin a day on the diet prescribed to keep the urine sugar-free. With loss in weight, the blood sugar content after fasting showed a consistent decrease, the carbohydrate tolerance gradually improved and finally the administration of insulin could be discontinued.

In cases 60, 66 and 83 there was a definite increase in the plasma cholesterol for two or three weeks after the institution of a low caloric diet. The possibility that this finding represents the so-called "starvation effect" will be discussed later.

COMMENT

The results reported in this paper do not lend themselves easily to statistical analysis for the following reasons: In a protracted study of this type in which a single constituent of the blood is investigated at more or less regular intervals for as long as sixty weeks, the existence of variables must be considered. The extent of weekly variations in the amount of blood cholesterol and the existence of seasonal variations, if any, and of premenstrual and menstrual changes are factors which cannot be ignored. The degree of diurnal variations of the blood cholesterol content found by Bruger and Somach ⁴ indicates that daily and weekly changes are probably marked. In 1924 Currie ⁵ maintained that marked seasonal variations exist; the presence of such variations, how-

4. Bruger, M., and Somach, I.: The Diurnal Variations of the Cholesterol Content of the Blood, *J. Biol. Chem.* **97**:23, 1932.

5. Currie, A. N.: The Cholesterol of Blood in Malignant Disease, *Brit. J. Exper. Path.* **5**:293, 1924.

TABLE 3.—*Effect of a Low Caloric Diet and Resultant Loss in Weight on the Plasma Cholesterol in Sixteen Cases of Obesity Complicated by Metabolic, Arthritic and Endocrine Disturbances**

Time, Weeks	Cholesterol	Weight	Diet	Time, Weeks	Cholesterol	Weight	Diet	Time, Weeks	Cholesterol	Weight	Diet
Case 56 (A)†				Case 66 (C)				Case 80 (D)			
0	326	192		0	348	168		0	274	175	
2	211	189	4	1	346	166	3	2	289	173	5
4	215	185	1	2	437	166	3	4	242	169	5
7	229	186	1	3	444	166	1	6	223	167	5
9	229	184	1	4	421	164	1	9	286	165	5
11	286	182	1	5	395	162	1				
13	190	179	1	6	399	164	1				
15	295	176	1	7	354	160	1				
17	204	176	1	9	303	157	1	Case 84 (E)			
23	253	176	1	12	286	158	1	0	168	197	
26	275	174	1	14	284	156	1	2	187	191	5
29	257	174	1	16	329	155	1	4	193	187	5
32	282	171	1	18	226	155	1	6	198	183	5
35	235	174	1	20	323	154	1	8	169	178	2
38	240	172	1	22	245	153	1	10	168	175	2
43	217	175	1	24	295	150	1	12	153	173	2
46	308	170	1Z	26	264	151	1†	14	207	170	2
48	253	169	1	28	315	148	1	18	210	167	2
50	295	172	1	30	185	145	1	20	190	166	2
52	232	168	1	32	201	144	1	22	187	166	2
54	252	168	1	35	242	140	1	27	205	162	2
56	250	168	1	38	266	144	1†	40	203	159	2
58	229	167	1	40	278	145	1†	42	192	159	5†
60	191	164	1	44	282	145	1†	46	175	160	6†
				53	233	152	1†	48	194	159	6†
								50	193	160	6†
Case 59 (A, B)				Case 71 (A)				Case 83 (D)			
0	229	187		0	278	188		0	274	173	
3	242	180	5	1	259	185	1	2	369	171	1
4	216	182	5†	3	235	187	1	4	354	169	1
6	282	178	5	7	245	184	1	6	252	168	1
8	214	175	5	9	308	180	1	8	227	171	7
11	218	175	5	14	293	177	1	13	227	170	5†
				16	280	176	1				
Case 60 (A, B)				Case 73 (B)				Case 85 (E)			
0	247	182		0	270	233		0	279	187	
1	285	175	Restricted	2	239	232	1	3	230	179	5
2	262	174	2	4	262	228	1	6	225	173	5
3	332	174	2	8	262	223	1	8	235	170	5
4	244	178	2†	17	282	221	1	13	178	165	5
5	391	175	2								
6	377	174	2								
7	364	176	2†								
8	344	171	1								
9	379	173	3					0	161	227	6
11	253	170	1					2	209	229	6
13	244	170	1†					4	180	224	1
15	244	170	1†					6	230	222	1
18	259	170	1†					8	255	218	1
20	276	169	1†					10	173	218	1†
22	272	170	1†					12	175	215	1
				0	178	225		19	202	210	1
				6	259	...	5	21	213	210	1†
				10	260	...	5	22	212	210	1†
				32	204	209	5†				
Case 62 (A)				Case 76 (A)				Case 92 (F)			
0	217	194									
2	217	190	None								
4	262	186	5								
13	242	180	5†								
Case 64 (B)				Case 77 (A)				Case 93 (G)			
0	260	168		0	181	298		0	289	280	6
1	248	168	5	11	166	268	1	2	198	271	7
4	216	164	5	17	161	260	1	4	174	265	7
9	255	164	5†	20	213	260	1	6	214	264	7
				24	195	255	1	9	216	256	7
				26	225	253	1	11	175	250	7
				28	232	257	1†	13	183	246	7
				30	218	252	1	16	233	238	7
				33	232	256	1†	20	259	234	7
								23	255	231	7
								27	200	231	7

* The associated clinical conditions are: (A) essential hypertension; (B) diminished dextrose tolerance curve; (C) diabetes mellitus; (D) osteo-arthritis; (E) rheumatoid arthritis; (F) hypovarian dysfunction; (G) acromegaly.

† This patient was taking food in excess of the prescribed diet.

ever, has been refuted by McEachern and Gilmour.⁶ Gonalons,⁷ Moynihan,⁸ quoting the work of Shiskin, and Okey and Boyden⁹ found definite changes immediately preceding and during menstruation. In view of these reports, it seemed futile to attempt a mathematical correlation between body weight and the blood cholesterol content; a study of the trend of the blood cholesterol content with diminishing body weight indicated that no such correlation existed.

Mention has been made that some subjects showed a distinct rise in the plasma cholesterol content for two or three weeks after the institution of a low caloric diet. The assumption was made that this increase may represent the so-called starvation effect. Starvation was found to increase the blood cholesterol in animals by Ellis and Gardner¹⁰ (rabbits), Rothschild¹¹ (rabbits), Morizawa¹² (rabbits), Mouriquand and Leulier¹³ (guinea-pigs), Shope¹⁴ (swine, cats, guinea-pigs and rabbits) and Wendt¹⁵ (dogs) and in human beings by Lennox, O'Connor and Bellinger¹⁶ (in one of three cases) and Shope¹⁴ (one case reported). The variable results reported by Lennox and his collaborators resemble closely our own findings, provided, of course, it

6. McEachern, J. M., and Gilmour, C. R.: Studies in Cholesterol Metabolism: II. Blood Cholesterol in Various Conditions, *Canad. M. A. J.* **26**:158, 1932.

7. Gonalons, G. P.: Variaciones de la colesterinemia durante el ciclo menstrual, *Semana méd.* **23**:639, 1916; Variations de la cholestérinémie pendant le cycle menstruel et la lithiase biliaire, *Bull. et mém. Soc. méd. d. hôp. de Paris* **41**:749, 1917; Litiasis biliar e hipercolesterinemia menstrual, *Rev. Asoc. méd. argent.* **26**:1091, 1917.

8. Moynihan, B.: Some Aspects of Cholelithiasis, *Brit. M. J.* **1**:393, 1925.

9. Okey, R., and Boyden, R. E.: Studies of the Metabolism of Women: III. Variations in the Lipid Content of Blood in Relation to the Menstrual Cycle, *J. Biol. Chem.* **72**:261, 1927.

10. Ellis, G. W., and Gardner, J. A.: The Origin and Destiny of Cholesterol in the Animal Organism: IX. The Cholesterol Content of the Tissues, Other Than Liver, of Rabbits Under Various Diets and During Inanition, *Proc. Roy. Soc. London, s.B* **85**:385, 1912.

11. Rothschild, M. A.: Zur Physiologie des Cholesterinstoffwechsels: V. Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand, *Beitr. z. path. Anat. u. z. allg. Path.* **60**:227, 1914-1915.

12. Morizawa, K.: Cholesteringehalt des Blutes von Hungerkaninchen, *Acta scholae med. Univ. imp. in Kioto* **7**:349, 1924-1925.

13. Mouriquand, G., and Leulier, A.: Inanition et cholestérine du sang et de quelques organes chez le cobaye, *Compt. rend. Soc. de biol.* **94**:533, 1926.

14. Shope, R. E.: Sugar and Cholesterol in the Blood Serum as Related to Fasting, *J. Biol. Chem.* **75**:101, 1927.

15. Wendt, H.: Lipidstoffwechselstudien am Hungertier, *Klin. Wchnschr.* **7**:2183, 1928.

16. Lennox, W. G.; O'Connor, M., and Bellinger, M.: Chemical Changes in the Blood During Fasting in the Human Subject, *Arch. Int. Med.* **38**:553 (Nov.) 1926.

is safe to assume that the ingestion of a low caloric diet (about 600 calories) by persons accustomed to a high caloric intake represents starvation in a relative sense.

CONCLUSIONS

The cholesterol content of the plasma in uncomplicated obesity and in obesity complicated by metabolic, arthritic or endocrine disease is not altered primarily by reduction in weight with a low caloric diet.

At times, the initial high plasma cholesterol content of the obese patient with complicating degenerative disease may show a significant decrease following reduction of weight on a low caloric diet. This fall in the blood cholesterol content is due not to a diminution in body weight but secondarily to changes in the clinical condition of the patient (improvement in carbohydrate tolerance in the obese patient with diabetes mellitus, onset of cardiac decompensation in the obese patient with hypertension, etc.).

In some obese subjects, the institution of low caloric diets is accompanied by a definite increase in the amount of plasma cholesterol for two or three weeks. The assumption is made that this elevation of the blood cholesterol content represents the so-called starvation effect, an observation that has been recorded previously in man and in animals.

EFFECT OF CERTAIN THERAPEUTIC MEASURES ON THE CARDIAC OUTPUT OF PATIENTS WITH CONGESTIVE HEART FAILURE

HARRY RESNIK JR., M.D.
NASHVILLE, TENN.

BEN FRIEDMAN, M.D.
NEW YORK

AND
T. R. HARRISON, M.D.
NASHVILLE, TENN.

An investigation of the change in the amount of blood pumped by the failing heart following the institution of a therapeutic procedure may be of interest from two points of view: (*a*) from the standpoint of the pathogenesis of congestive heart failure and (*b*) from the standpoint of the mechanism whereby a given procedure produces improvement. The present study was undertaken with the idea of elucidating the first of these problems, but certain information concerning the second question has also been obtained.

METHOD

The subject—in the basal state—was brought to the laboratory in a wheelchair. The consumption of oxygen was determined in duplicate by analyses of samples of the expired air which was collected in a Tissot spirometer. The arteriovenous oxygen difference was measured by the three sample acetylene technic. Two rebreathings were usually done, the samples being procured at approximately twenty, twenty-four and twenty-eight seconds in the first, and two seconds later in the second. When the two successive values for the arteriovenous difference obtained during a single rebreathing failed to agree within 10 per cent, the determination was discarded. Further details of the technic employed are given in previous studies.¹

Following one or more measurements of the cardiac output the desired therapeutic procedure was instituted. In those cases in which the effect of rest was studied the subject was kept in bed, fluids were restricted and no medication was administered other than sedatives when necessary and maintenance doses of digitalis when the subject had already been receiving this drug. After several days of this regimen the measurements were repeated. A similar plan was fol-

From the Department of Medicine, Vanderbilt University School of Medicine.

1. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, *J. Clin. Investigation*, 7:751, 1933. Harrison, T. R.; Friedman, B.; Clark, G., and Resnik, H., Jr.: Cardiac Output in Relation to Cardiac Failure, *Arch. Int. Med.* 54:238 (Aug.) 1934.

lowed in the case of the other therapeutic procedures. In the observations on the effect of venesection, several measurements of the cardiac output were made in one day, and some of the determinations were made several hours after the ingestion of a glass of milk. With these exceptions all observations were made on the subject in a strictly basal state.

RESULTS

Rest.—In table 1 are shown the data on four patients. Following two or more days of rest the vital capacity rose in three subjects, and diuresis occurred in two. Subjective improvement occurred in three of the four patients. A significant decline in oxygen consumption occurred in one instance. The cardiac output decreased in two of the subjects. In proportion to the metabolism the cardiac output decreased in two persons and was unchanged in the others. (Alterations in the cardiac output and in the arteriovenous oxygen difference of less than 10 per cent are not considered significant, for the error of the method may be this great.) No correlation existed between clinical improvement and the changes in cardiac output.

The changes in cardiac output and in oxygen consumption which occurred following rest are not to be ascribed to the patients' becoming accustomed to the procedures involved, for the subjects had been trained to the methods prior to the beginning of our observations.

Venesection.—Four observations were made on three patients (table 2). Each subject claimed that dyspnea was benefited by the procedure. The vital capacity tended to be greater and the ventilation to be less following bleeding. The cardiac output per minute was decreased in three of the four observations. A temporary decrease in this function in proportion to the metabolism was observed in three instances and the reverse effect in one.

Two striking effects of venesection were noted. The subjects were bled while sitting in a wheelchair. Two of them fainted. As circulatory collapse came on, each subject mentioned that he felt less dyspneic. It was interesting to note that the congestive manifestations—venous distention and dyspnea—became less marked as the phenomena of peripheral circulatory failure—weakness, pallor and fainting—became more marked. In the subjects who fainted, a striking decline in the cardiac output occurred.

Another surprising effect of venesection, which occurred in three of the four observations, was a sharp decrease in the oxygen consumption. This was most striking in the two subjects who prior to bleeding had a marked elevation in the metabolic rate. In order to study this phenomenon more closely, observations were made of the effect on the oxygen consumption of reinfusion of the previously removed blood

TABLE 1.—Effect of Rest on the Cardiac Output and on the Other Functions of Patients with Congestive Heart Failure

Subject	Diagnosis	Date	Dyspnea*	Edema	Body Weight, Pounds	Vital Capacity, Liters	Cardiac Output per Minute, Ce.	Oxygen Consumption per Liter, Ce.	Arterio-venous Oxygen Difference, Ce.	Cardiac Output per Minute, Liters	Clinical Improvement
A. M.	Syphilitic aortic insufficiency.....	10/14/33 10/16/33	+++ ++	++ ++	179 173	2.35 2.60	92 84	271 245	128 120	2.11 2.04	Definite
G. M.	Syphilitic myocarditis.....	9/ 7/33 9/13/33	++ +	++ +	150 137	1.75 2.10	75 78	232 241	66 75	3.49 3.19	Definite
A. T.	Mitral stenosis.....	7/22/33 7/25/33	++ +	++ ++	96 96	1.70 1.80	82 100	186 200	87 107	2.13 1.83	Questionable
R. O.	Hypertension.....	2/18/33 2/22/33	++ +	0 0	136 135	2.75 2.70	82 88	187 178	68 71	2.74 2.41	None

* In this and the following tables the symbols +, ++ and +++ refer respectively to dyspnea on exertion only, mild dyspnea at rest, and moderate dyspnea at rest.

TABLE 2.—Effect of Venesection on the Cardiac Output and Other Functions of Patients with Congestive Heart Failure

Subject	Diagnosis	Date	Dyspnea	Edema	Time in Relation to Venesection	Vital Capacity, Liters	Ventilation per Minute, Liters	Oxygen Arterio-venous Consumption per Liter, Ce.	Cardiac Output per Minute, Liters	Clinical Improvement	Comment
F. B.	Syphilitic aortic insufficiency	6/27/33	+++ ++	++ ++	Before 30 min. after 2 hr. after 6 hr. after 1 day after	1.85 ... 1.90 1.90 1.90	15.2 12.6 12.5 14.8 13.5	463 374 324 351 362	110 109 95 112 120	Slight Slight Slight Slight	500 cc. blood removed
L. W.	Mitral stenosis.....	6/21/33 6/22/33	+++ +++	++ ++	Before Before 40 min. after 2 hr. after 8 hr. after	2.85 2.90 3.10 3.25 3.30	8.3 9.5 10.7 9.8 8.7	235 240 292 194 233	72 75 86 72 73 Marked Marked	500 cc. blood removed; patient fainted immediately after
		8/ 1/33	+++	++	Before 30 min. after 1 hr. after 1 day after	2.95 3.15 3.10 3.00	6.8 7.3 6.9 8.7	197 202 203 239	74 82 82 71	Moderate Moderate Slight	565 cc. blood removed
M. O.	Hypertension.....	8/14/33 8/15/33	++ +	++ ++	Before 90 min. after 3 hr. after 1 day after	3.70 3.70 3.70 3.90	10.8 8.9 8.7 12.6	331 327 227 353	96 112 105 99	Slight Moderate	350 cc. blood removed; patient fainted

(fig. 1). In the one patient so studied venesection caused a sharp diminution in the oxygen consumption, which returned to the previous level following the administration of the blood. (Further discussion of the mechanism of the changes in metabolic rate in relation to venesection is beyond the scope of this paper. The problem is dealt with in more detail in a publication by Resnik and Friedman.²)

Morphine.—Two subjects were studied. In each instance the dyspnea, moderately severe before treatment, was relieved. The pulse rate diminished somewhat, the ventilation declined sharply. Parallel diminution of oxygen consumption and cardiac output occurred, the arteriovenous oxygen difference being unaffected (table 3).

Quinidine.—Three sets of observations were made on two patients who had auricular fibrillation and minimal congestive failure (table 4).

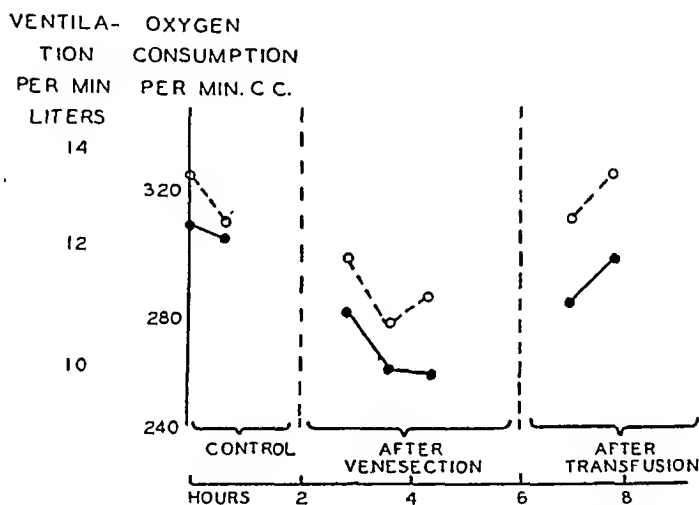


Fig. 1 (F. B.).—Venesection produced a marked decrease in the ventilation and in the oxygen consumption of the patient with syphilitic aortic insufficiency. When the blood which had been removed was reinfused, these effects were reversed. The white circles joined by lines indicate the ventilation per minute; the black circles, the oxygen consumption per minute.

In each instance the administration of quinidine was followed by restoration of the normal mechanism and an increase in the cardiac output. These results are similar to those reported by Smith, Walker and Alt,³

2. Resnik, H., Jr., and Friedman, B.: Studies on the Mechanism of the Increased Oxygen Consumption in Persons with Cardiac Disease, *J. Clin. Investigation* **14**:551, (Sept.) 1935.

3. Smith, W. C.; Walker, G. L., and Alt, H. L.: The Cardiac Output in Heart Disease: I. Complete Heart Block, Auricular Fibrillation Before and After Restoration to Normal Rhythm, Subacute Rheumatic Fever, and Chronic Valvular Disease, *Arch. Int. Med.* **45**:706 (May) 1930.

TABLE 3.—Effect of Morphine on the Cardiac Output and on the Other Functions of Patients with Congestive Heart Failure

Subject	Diagnosis	Date	Dyspnea	Edema	Vital Capacity, Liters	Ventilation per Minute, Liters	Arterio-venous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Comment
A. M.	Syphilitic aortic insufficiency	1/ 9/34	++ +	++ ++	2.60 2.70	74 70	2.33 2.17	Before morphine Two hours after 0.02 Gm. morphine
F. B.	Syphilitic aortic insufficiency	2/28/34	+++ +	+++ +	1.50 1.50	11.3 8.6	103 96	2.62 2.41	Before morphine One hour after 0.015 Gm. morphine

TABLE 4.—Effect of Quinidine on the Cardiac Output and Other Functions

Subject	Date	Dyspnea	Edema	Vital Capacity, Liters	Heart Rate	Pulse Rate	Oxygen Consumption per Minute, Cc.	Arterio-venous Oxygen Difference per Liter, Cc.	Cardiac Output per Minute, Liters	Comment
R. R.	9/12/33	+	0	3.30	76	76	311	89	3.50	Fibrillating Before administration of quinidine
	9/13/33	+	0	3.30	80	80	283	90	3.14	Receiving quinidine Regular Premature beats Regular
	9/14/33	+	0	3.50	76	76	232	87	3.26	
	9/18/33	+	0	3.50	66	66	267	60	4.41	
	9/19/33	+	0	3.10	79	79	255	65	3.95	
	9/20/33	+	0	3.45	66	66	260	67	3.85	Receiving quinidine Before digitalization Before digitalization Before digitalization
	2/ 2/34	++	0	3.00	124	102	366	99	3.10	
	2/ 5/34	+	0	3.45	88	88	235	100	2.85	
	2/ 8/34	+	0	3.45	80	80	271	89	3.03	
	2/12/34	+	0	3.50	56	56	251	77	3.24	Receiving quinidine Before digitalization Before digitalization
	2/15/34	+	0	3.50	64	64	283	80	3.53	
	2/20/34	+	0	3.20	61	64	265	69	3.53	Receiving quinidine Before digitalization
L. L.	5/ 4/33	++	0	2.10	72	72	179	89	2.90	Digitalized throughout Before digitalization Before digitalization
	5/ 6/33	+	0	2.20	72	72	180	82	2.18	
	5/ 8/33	+	0	2.35	76	76	196	84	2.33	

using the carbon dioxide method, and by Kerkhof and Bauman,⁴ with the two sample acetylene technic. In proportion to the metabolism the change in cardiac output was slight in subject L. L. but was striking at the time of each observation in subject R. R. In the second group of observations on the latter subject it is interesting to note that clinical improvement, as shown by rise in vital capacity and decrease in dyspnea, occurred following the administration of digitalis without a significant change in the cardiac output. (This is in accord with our previous findings with digitalis.⁵) The increase in cardiac output which followed the administration of quinidine was not accompanied by any striking clinical effect other than the change in rhythm.

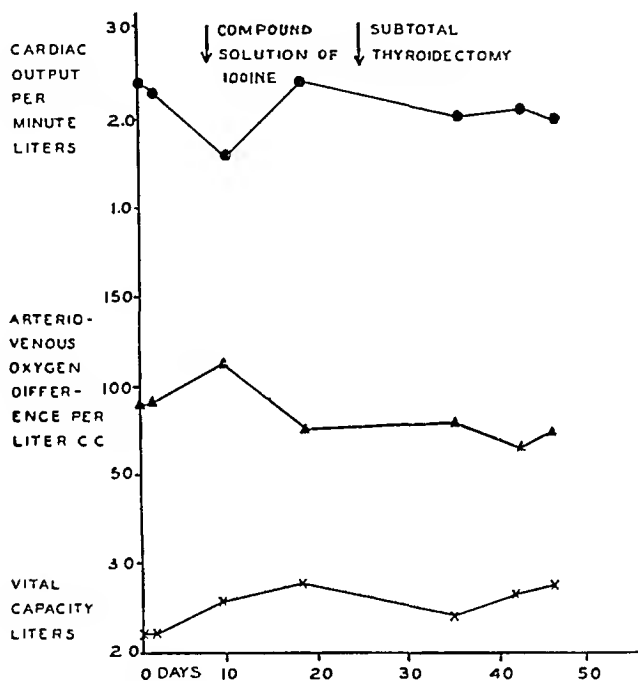


Fig. 2 (A. C.).—The administration of compound solution of iodine was followed by a temporary decline in the cardiac output of the patient with thyrotoxicosis. Following partial thyroidectomy the output again declined and remained below the preoperative level. In proportion to the metabolism the cardiac output increased after the operation. The rise in vital capacity paralleled the clinical improvement.

Subtotal Thyroidectomy.—One patient who had cardiac failure secondary to thyrotoxicosis was studied (fig. 2). After the administration

4. Kerkhof, A. C., and Bauman, H.: Minute Volume Determinations in Mitral Stenosis During Auricular Fibrillation when Restored to Regular Rhythm, *Proc. Soc. Exper. Biol. & Med.* **31**:168, 1933.

5. Friedman, B.; Clark, G.; Resnik, H., Jr., and Harrison, T. R.: Effect of Digitalis on the Cardiac Output of Persons with Congestive Heart Failure, *Arch. Int. Med.*, to be published.

of compound solution of iodine, U. S. P., there was a marked temporary decline followed by a rise in the cardiac output. After subtotal thyroidectomy the cardiac output was slightly less, but considerably greater in proportion to the metabolism, than before the operation. Clinical improvement, as shown by decrease in dyspnea and rise in vital capacity, was striking after the administration of compound solution of iodine and persisted after the operation.

Total Thyroidectomy.—Levine,⁶ Blumgart⁷ and their co-workers recommended total ablation of the thyroid gland in persons with irreducible congestive heart failure. In this clinic only one patient has been so treated.

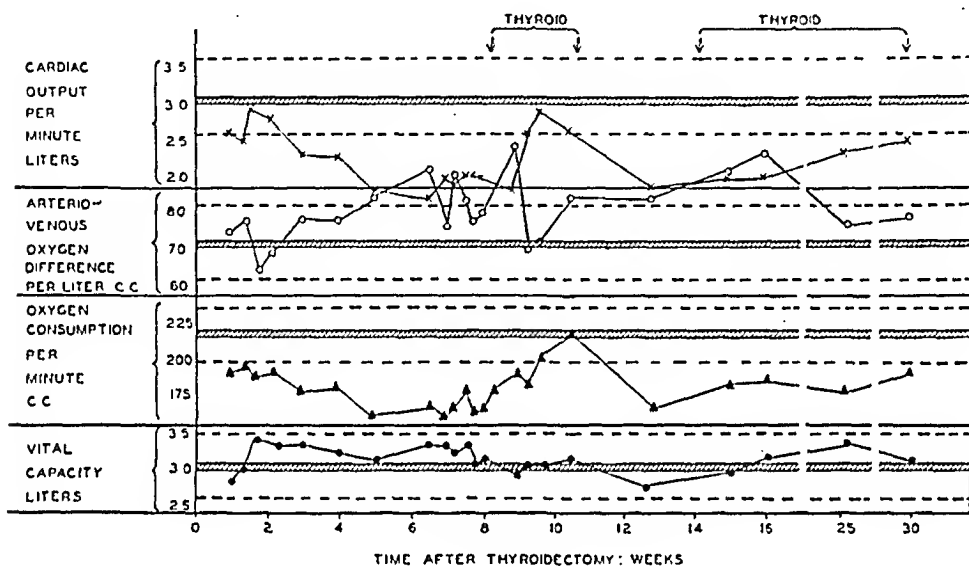


Fig. 3.—The shaded areas represent the averages and the dotted lines indicate the ranges of the various functions in the fifteen observations made before operation. All the points charted designate postoperative measurements. Following total thyroidectomy the vital capacity tended to be somewhat greater. The oxygen consumption and the cardiac output were considerably diminished. The changes in the arteriovenous oxygen difference were inconstant, but this function tended to be somewhat increased, indicating a diminution in the cardiac output in proportion to the metabolism.

6. Levine, S. A.; Cutler, E. C., and Eppinger, E. C.: Thyroidectomy in Treatment of Advanced Congestive Heart Failure and Angina Pectoris, *New England J. Med.* **209**:667, 1933.

7. Blumgart, H. L.; Levine, S. A., and Berlin, D. D.: Congestive Heart Failure and Angina Pectoris: The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity, *Arch. Int. Med.* **51**:866 (June) 1933; Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, *ibid.* **52**:165 (Aug.) 1933.

L. W., a 52 year old mechanic, was first admitted to the Vanderbilt University Hospital in March 1931, complaining of orthopnea, paroxysmal dyspnea and slight edema of the legs of one month's duration. The patient had rheumatic fever at the age of 20 at which time he was told that his heart had been affected. He was free from symptoms until June 1930, when he began to have dyspnea on exertion, gradually becoming more severe. At the time of entry there was evidence of rheumatic heart disease with mitral stenosis, auricular fibrillation and cardiac enlargement.

With digitalization he had temporary improvement, but the symptoms returned with such severity as to require hospitalization in October 1931. In July 1932 he reentered the hospital, because of orthopnea, paroxysmal dyspnea, cough and expectoration, and in addition to cardiac decompensation his condition was diagnosed as bronchopneumonia, which resulted in a rather extensive bronchiectasis.

In June 1933 he was admitted again, because of congestive heart failure, but three weeks after discharge further hospitalization was found necessary. Again relief was very temporary, and in August 1933 he was readmitted for the fifth time, because of cardiac decompensation.

Despite restriction of activity, limitation of fluids and the use of digitalis and diuretics, it was apparent that the patient's cardiac reserve had diminished to such an extent that he was unable to remain at home in comfort, although in the hospital it was possible to keep him comparatively free from symptoms. As another therapeutic measure total ablation of the thyroid was proposed, the risk of which the patient readily consented to undertake. On Sept. 12, 1933, this operation was performed by Dr. Alfred Blalock.

After one week the patient felt so much improved that he was able to sleep almost flat in bed after being up and about for most of the day. This improvement persisted until the end of October 1933, when he began to have paroxysms of dyspnea, slight edema, drowsiness and abdominal distention. With hospitalization and the temporary administration of small doses of thyroid extract, he showed considerable improvement. Three weeks after discharge, on Dec. 14, 1933, readmission was considered advisable because of a recurrence of severe dyspnea, and again in January 1934 it was necessary to hospitalize the patient for treatment of cardiac decompensation as well as profound hypothyroidism. He then entered on a period of five months during which time his distressing symptoms disappeared, except for slight dyspnea and edema that did not prevent him from being up and about all day at home or from taking brief walks outdoors. During this interval he received small doses of thyroid extract, and although he had evidence of cardiac failure he was much more comfortable than he had been during the four months prior to operation, at which time his condition was becoming progressively worse. In May 1934 the dyspnea again became severe enough to require hospitalization.

The patient appeared to be improved following the operative procedure. The beneficial effects were not remarkable but were definite. His vital capacity was slightly greater, and his ventilation was definitely less than before the procedure. The quotient $\frac{\text{ventilation}}{\text{vital capacity}}$, which has been shown⁸ to run parallel to the degree of cardiac dyspnea, was diminished by the procedure, and he complained less of dyspnea.

8. Harrison, T. R.; Turley, F. C.; Jones, E., and Calhoun, J. A.: Congestive Heart Failure: X. The Measurement of Ventilation as a Test of Cardiac Function, *Arch. Int. Med.* 48:377 (Sept.) 1931.

Of especial interest are the changes in oxygen consumption and in cardiac output. The former declined from the average preoperative value of 220 to 160 cc. per minute. During this period, an even greater decrease in cardiac output occurred, the arteriovenous oxygen difference being somewhat greater than the average value before operation. Thyroid was then given, and the oxygen consumption and the cardiac output increased to their preoperative levels. When replacement therapy was discontinued, the values again declined. Readministration of thyroid, in smaller doses, was followed by a slight increase in the oxygen consumption and in the cardiac output. The optimum level for these functions appeared to be about 20 per cent below the preoperative values.

Abdominal Paracentesis.—One patient was studied (table 5). After the withdrawal of fluid from the abdomen the patient experienced marked relief from dyspnea. The associated decline in oxygen consumption was probably due to the diminution in respiratory effort. A parallel decrease in cardiac output occurred. In this connection, it is interesting to note that Brams and Golden⁹ demonstrated a decline in venous pressure following abdominal paracentesis in patients with cirrhosis of the liver.

Resection of the Pericardium.—A subject with obliterative pericarditis, which led to an increase in venous pressure and congestive phenomena, was studied before and after partial resection of the pericardium. The history of this patient is being reported in detail by Burwell and Flickinger.¹⁰ Before operation he was bedridden because of anasarca. Following the removal of a portion of the pericardium by Dr. Alfred Blalock marked improvement occurred, and he is now able to lead a relatively normal life. His improvement has been attended by a decline in the arteriovenous oxygen difference and a marked increase in the cardiac output (table 5).

COMMENT

The observations which have been cited show clearly that the fundamental physiologic alteration responsible for the clinical manifestations of congestive heart failure is not a decrease in the cardiac output, either actually or in proportion to the metabolic needs. When improvement is due to certain therapeutic measures, it may be associated with an increase in this function, but when it is brought about by other procedures, it is associated with the reverse effect. At first sight it may seem surprising that two different measures may each produce benefit and yet apparently exert opposite physiologic effects. There are, however, certain considerations which tend to resolve this apparent paradox.

9. Brams, W. A., and Golden, J. S.: Observations on the Vascular Response to Drainage of Ascites, *J. Lab. & Clin. Med.* **19**:948, 1934.

10. Burwell, C. S., and Flickinger, Don: Obstructing Pericarditis: Effect of Resection of the Pericardium on the Circulation of a Patient with Concretio Cordis, *Arch. Int. Med.* **56**:250 (Aug.) 1935.

TABLE 5.—*Effect of Abdominal Paracentesis and of Cardiac Decortication on the Cardiac Output and Other Functions*

Subject	Diagnosis	Therapeutic Procedure Studied	Date	Dyspnea	Anasarca	Vital Capacity, Liters	Heart Rate	Oxygen Consumption per Minute, Cc.	Arterio-venous Oxygen Difference per Cc.	Cardiac Output per Minute, Liters	Comment
A. T.	Rheumatic mitral disease	Abdominal paracentesis, 3,000 cc.	8/ 4/33	+++	+++	1.85	64	195	93	2.10	Before paracentesis
			8/ 4/33	+	+	*	69	101	101	1.59	6 hours after paracentesis
			8/ 5/33	+	+	*	64	109	91	1.82	1 day after paracentesis
H. O.	Concretio cordis (obliterative internal pericarditis)	Cardiac decortication	11/24/33	++	+++	2.00	—	207	96	2.16	Before operation
			11/27/33	++	+++	2.00	116	217	104	2.09	
	(Partial resection of the thickened pericardium)		1/27/34	+	+	*	118	235	92	2.54	After operation, gradual improvement
			2/ 3/34	+	+	*	118	233	74	3.16	
			2/ 6/34	+	+	*	114	228	80	2.86	
			2/21/34	0	±	2.10	108	271	72	3.79	

* The vital capacity could not be measured accurately because of the pain produced in the wound by breathing.

Aside from pericardial resection, which is employed for a condition which differs both anatomically and functionally from the usual type of congestive heart failure, the therapeutic measures which have been studied appear to fall into three groups:

1. After certain procedures improvement is accompanied by a decrease in the work¹¹ of the heart. Examples of such procedures are rest, venesection, sedatives, as exemplified by morphine, and abdominal paracentesis. These measures tend to decrease the respiratory effort by diminishing the ventilation directly (morphine), by lowering the metabolism (rest) or by decreasing the reflex stimulation of breathing (venesection or abdominal paracentesis). The lessened respiratory effort tends in itself to decrease the oxygen consumption, as has been shown by Resnik and Friedman.² In severely dyspneic patients the decline in metabolism so produced may be of considerable magnitude. Aside from the decline in metabolism, these various therapeutic measures may lessen the work of the heart by causing a decrease in the venous return and in the cardiac output in proportion to the metabolism.

2. After certain other procedures improvement is accompanied by what appears to be an increase in the mechanical efficiency of the heart. Thus, the reversion to the normal mechanism following the administration of quinidine tends to make the heart more efficient because pulse deficit is eliminated and the rate is slowed, and possibly also because auricular contraction is reestablished.¹² Similarly, the most important effect of digitalis appears to be, as has been pointed out elsewhere,⁵ its action in increasing cardiac efficiency.

3. It is probable that after some therapeutic measures benefit is accompanied both by decrease in the work of the heart and by increase in its efficiency. Thyroidectomy diminishes the work performed by the

11. The work of the heart is not dependent on the output alone. The blood pressure and the velocity imparted to the blood are also factors. However, the velocity is, under conditions of low output, of minor import. Since our patients have not shown an increase in blood pressure as improvement occurred—the reverse effect has sometimes been observed—it is justifiable to speak of a decrease in work when the output has declined.

12. The effect of a pulse deficit in making the heart inefficient is obvious, for each beat which does not reach the periphery is wasted. For a given amount of work per minute the heart is more efficient at slow than at rapid rates, because during tachycardia the semilunar valves have to be opened more frequently and the energy so expended is not used in expelling blood. It has been demonstrated by Evans and Matsuoka that the oxygen consumed by the heart is greater at rapid than at slow rates, the amount of work being kept constant (Evans, C. L., and Matsuoka, Y.: The Effect of Various Mechanical Conditions on the Gaseous Metabolism and Efficiency of the Mammalian Heart, *J. Physiol.* 49:378, 1915).

heart, and the slower cardiac rate after the operation would be expected to produce an increase in mechanical efficiency.

The energy expended by the heart is related to two factors: the work accomplished and the efficiency of performance. If the latter remains constant, then any decrease in work will be associated with a decrease in expenditure of energy. We have shown that the output and hence, in all likelihood, the work of the heart are decreased by certain therapeutic procedures. It is probably justifiable to assume that the decrease in work is accompanied by a diminution in the energy expended by the heart. Other effective therapeutic measures do not decrease the cardiac work but may even increase it somewhat. However, it is probable that these measures increase the mechanical efficiency and thereby diminish the energy expended. If this is true, it would appear that all the therapeutic measures which are useful in treating congestive heart failure have one fundamental action in common—they tend to rest the heart.

The reasoning which has led to this conclusion rests on a number of assumptions. However, it is supported by strong evidence, which is as follows: It has been amply shown both clinically (Stewart and Cohn¹³ and experimentally (Patterson, Piper and Starling¹⁴) that heart failure is associated with cardiac dilatation and that improvement is accompanied by diminution in the size of the heart. According to Starling and Visscher,¹⁵ whose findings were confirmed by Hemmingway and Fee,¹⁶ the energy expended by a heart is proportional to its diastolic volume, regardless of the work accomplished. If this law is applicable to man, then it is evident that any measure which produces a decrease in the degree of cardiac dilatation will reduce the energy expended by the heart (provided, of course, that it does not increase the pulse rate). Since practically all measures which produce clinical improvement do decrease the size of the heart, it may be assumed that they diminish its expenditure of energy. We believe that this is the chief effect of all the various therapeutic measures which are useful in the treatment of heart failure. They tend to rest an overstrained organ.

Congestive phenomena occurring in persons with *concretio cordis* are due to a mechanism which is different from that responsible for heart failure of the ordinary type. The thickened pericardium prevents

13. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: II. The Effect on the Output in Normal Human Hearts; Effect on Output of Hearts in Heart Failure with Congestion in Human Beings, *J. Clin. Investigation* **11**:917, 1932.

14. Patterson, S. W.; Piper, H., and Starling, E. H.: The Regulation of the Heart Beat, *J. Physiol.* **48**:465, 1914.

15. Starling, E. H., and Visscher, M. B.: Regulation of the Energy Output of the Heart, *J. Physiol.* **62**:243, 1922.

16. Hemmingway, A., and Fee, A. R.: Relationship of the Volume of the Heart and Its Oxygen Usage, *J. Physiol.* **63**:299, 1927.

filling and hence limits the energy which the heart can expend. Under such conditions the heart cannot dilate sufficiently to carry on the circulation adequately. Resection of the pericardium allows the heart to perform more work. In patients with obliterative pericarditis a condition of true cardiac insufficiency exists, for the heart is unable to expend sufficient energy. In the usual type of congestive failure the condition is rather that of cardiac inefficiency, for the heart can perform its work, but only at the price of a wasteful expenditure of energy.

SUMMARY

The cardiac output per minute of persons with congestive heart failure tends to be decreased by rest, venesection, morphine, thyroidec-tomy and abdominal paracentesis. In proportion to the metabolic needs the output may or may not be diminished by these procedures.

In patients with auricular fibrillation the restoration of the normal rhythm with quinidine has been associated with an increase in the cardiac output.

Resection of the pericardium of a patient with obliterative pericarditis was followed by an increase in the cardiac output.

The mechanism of improvement produced by the various therapeutic measures has been discussed. It is concluded that pericardial resection produces improvement in patients with concretio cordis by allowing the heart to do more work. On the other hand, therapeutic benefit in heart failure of the ordinary type is believed to be dependent on one fundamental factor: rest of the heart as a result of diminished expenditure of energy. Such an effect may be brought about either (*a*) by procedures which diminish the work done by the heart or (*b*) by measures which increase its mechanical efficiency so that less energy is wasted.

EFFECT OF HIGH INTRAPLEURAL PRESSURE ON BLOOD PRESSURE

JEROME R. HEAD, M.D.

CHICAGO

The purpose of the present paper is to report rather than to explain certain observations on the effects of increased intrapleural pressure on the blood pressure. The clinical picture resulting from an increase in pressure in the pleural cavity is sufficiently definite to be termed a syndrome, and although in my experience this syndrome has been observed commonly, it has only been hinted at in the literature and is generally unknown and unrecognized. I can best present its characteristics by reporting the cases which first called it to my attention.

REPORT OF CASES

Miss E. C. was seen in consultation with Dr. O'Neill at the Evanston Hospital on Aug. 4, 1931. Five days previously, in an automobile accident, she had suffered a severe injury to the right side of the thorax. A roentgenogram showed that five ribs on the right side were broken and that the right pleural cavity was filled with fluid and air. For the first few days the temperature was elevated to from 100 to 101 F. It then fell to 98 F., and at the same time the pulse rate rose from 110 to 120. When I first saw the patient she presented a picture characteristic of traumatic shock. There was marked pallor, the extremities were cold and the body was covered with beads of perspiration. The pulse rate was 120, and the respiratory rate was 26. Breathing was shallow and grunting. The pulse, which was extremely small, disappeared almost completely on inspiration.

The blood pressure on expiration was 102 systolic and 72 diastolic. During inspiration no reading could be obtained at any level. The pressure in the pleural cavity was +28 cm. of water. After 525 cc. of pure blood was removed, the pressure in the pleural cavity was lowered to 11 cm., and a definite and dramatic change was produced in the patient's condition: The pallor disappeared, the extremities became warm, and the sweating stopped abruptly. The pulse increased in volume, and the rate fell to 100. The expiratory blood pressure rose to 112 systolic and 72 diastolic. The inspiratory systolic pressure was now 90. By the next day the original symptoms and signs had returned. The expiratory blood pressure was 84 systolic and 60 diastolic. There was no inspiratory pressure. The pressure in the pleural cavity was +12 cm. of water. After the removal of 900 cc. of blood, air was injected into the pleural cavity until the pressure was +8. The picture was again reversed; the blood pressure was then 112 systolic and 65 diastolic.

A similar picture was presented by a patient seen in consultation with Dr. Keaton and Dr. Mussil at the St. Francis Hospital (Evanston). A man, 28 years old, had had spontaneous pneumothorax complicated by spontaneous hemorrhage into the pleural cavity. I saw him a week after the onset. Pallor, diaphoresis and coldness of the extremities were marked. The pulse rate was 120, and the respiratory

rate, 30 per minute. The expiratory blood pressure was 110 systolic and 90 diastolic. There was no inspiratory pressure. The pressure in the pleural cavity was + 30 cm. of water. The withdrawal of 1,500 cc. of practically pure blood lowered the pressure to + 4 cm. The pallor disappeared, and the sweating stopped immediately. The pulse rate fell to 110. The systolic blood pressure rose to 120, and the diastolic pressure fell to 80. There was still a difference between the inspiratory and the expiratory pressure, but it was less marked than before the aspiration.

In both of these cases there was a combination of hemorrhage and of high pressure in the pleural cavity. In both there was a definite lowering of the blood pressure with a marked fall during inspiration. While the expiratory blood pressure was well above that usually productive of signs and symptoms of circulatory failure (shock), definite shock was present. The mean blood pressure evidently was below the critical level. In both cases lowering the intrapleural pressure by aspi-

TABLE 1.—*Effects of Changes in Intrapleural Pressure*

	Intrapleural Pressure, Cm. of Water		Systolic Pressure, Mm. of Mercury		Diastolic Pressure, Mm. of Mercury
	Inspira- tory	Expira- tory	Expira- tory	Inspira- tory	
Mr. J. (right pneumothorax)					
Before injection.....	-6	-2	130	130	90
After injection of 800 cc. of air....	-1	+2	155	130	90
Mr. W. (left pneumothorax)					
Before injection.....	-2	+8	140	120	80
500 cc. of air removed.....	-8	-0	120	120	80
500 cc. of air injected.....	-2	+8	120	120	80
One hour later.....	-2	+8	140	120	80
Mrs. G. (left pneumothorax)					
Before injection.....	-2	+6	145	120	85
500 cc. of air removed.....	-8	-1	120	120	80
500 cc. of air injected.....	-2	+6	140	120	85

rating fluid raised the blood pressure, decreased the discrepancy between its inspiratory and expiratory phases and brought about the immediate disappearance of the symptoms of circulatory collapse.

I have since observed this discrepancy between the inspiratory and the expiratory blood pressure in patients with pleurisy with effusion and with both spontaneous and artificial pneumothorax. It occurs only when the pressure in the pleural cavity is positive. In some cases the mean blood pressure is raised; in others, lowered. A serious drop occurs only when the intrapleural pressure is very high or there is some complicating factor, such as hemorrhage. One is usually able to detect the variation by palpating the radial artery, and in extreme cases complete absence of pulsation during inspiration is occasionally noted. The phenomenon is produced by compression of either the right or the left lung. If the breath is held on inspiration, the blood pressure gradually rises and comes through at a higher level, but only after considerable delay.

Table 1 shows the effects of raising and of lowering the intrapleural pressure in different patients with artificial pneumothorax. I did not feel justified in producing extremely high pressures for purely experimental purposes.

The observations and syndrome reported are of frequent occurrence and of real importance. In cases of pleurisy with effusion and of spontaneous and artificial pneumothorax the fall in the blood pressure on inspiration indicates definite cardiorespiratory embarrassment, and a lowering of the blood pressure on expiration points to a condition which may lead rapidly to circulatory failure and death. It is important to know that even when there is an expiratory pressure of over 100 mm. of mercury, the mean pressure may be below the critical level for shock. In cases of hemorrhage into the pleural cavity it is important to know that both the loss of blood and the rising intrapleural pressure tend to lower the blood pressure and that the collapse incident to it may be immediately relieved by reducing the pressure in the pleural cavity.

I have been able to find but one clinical reference to this exaggerated variation in the volume of the pulse in cases of increased intrapleural pressure: Rosenbach¹ in 1886 noted an inspiratory weakening or disappearance of the radial pulse in cases of massive pleural effusion. He suggested that it was caused by the closure of the vena cava by the contraction of the diaphragm. That his surmise was incorrect is shown by the fact that in one of my cases the diaphragm had been paralyzed. Many other writers have noted a weak, rapid and irregular pulse. Two other observations which bear directly on the cases reported and which can therefore best be mentioned at this point are as follows: In Starling's² textbook on physiology it is stated that acute hemorrhage frequently produces a marked exaggeration of the Traube-Hering waves, and Frantzel³ noted clinically that when there is an increase in the intrapleural pressure the blood pressure rarely falls unless there are complicating factors.

The physiologic problems involved are numerous and intricate and are concerned with the whole field of respiration and circulation and the mechanical and the reflex factors which influence them.

Changes in blood pressure synchronous with the phases of respiration are normal. Known generally as the Traube-Hering waves, they have been the subject of numerous and extensive investigations. The

1. Rosenbach, O.: *Virchows Arch. f. path. Anat.* **105**:215, 1886.

2. Starling, E. H.: *Principles of Human Physiology*, ed. 6, Philadelphia, Lea & Febiger, 1933.

3. Frantzel, cited by Lieven, P.: *Ueber den Blutdruck bei den verschiedenen Formen des Pneumothorax*, Dorpat, H. Laakmann, 1893.

literature on the subject has been thoroughly reviewed by Tigerstedt.⁴ On inspiration there is a primary fall and a secondary rise of blood pressure, and on expiration, a primary rise and a secondary fall. The secondary rise on inspiration and the fall on expiration become apparent only if respiration is slow, and both signs are absent if the pericardial sac is open to atmospheric pressure. This indicates that the secondary changes are caused by variations in the pressure on the heart and on the intrathoracic vessels.

There are two possible explanations of the Traube-Hering phenomenon, the one mechanical and the other reflex. Tigerstedt listed all the factors concerned, as shown in table 2.

The mechanical explanation is the simplest and most tempting, but experimental evidence suggests that it is less important than the reflex explanation. It is easy to argue that at the beginning of inspiration

TABLE 2.—*Factors Concerned with the Traube-Hering Phenomenon*

	Inspiration	Expiration
1. Suction of blood toward the heart.....	Increased	Decreased
2. Diastole of heart.....	Easier	Harder
3. Systole of heart.....	Harder	Easier
4. Diameter of pulmonary vessels.....	Increased	Decreased
5. At change to the other phase of respiration, blood remains in vessels of lung or is forced out of them	Remains back	Forced out
6. During this phase of respiration the blood flow through the pulmonary vessel is	Easier	Harder
7. Then as a result of factors 4 and 6 the blood flow to the left heart is	First decreased, then increased	First increased, then decreased
8. The pulse rate with the vagus nerves intact.....	Increased	Decreased
9. The vessels of the systemic circulation are.....	Wider	Narrower
10. The pressure in the abdominal cavity is.....	Increased	Decreased

the rapid increase in the size of the pulmonary bed causes a temporary delay of blood flow to the left heart and a fall in resistance in the pulmonary circuit but the increased aspiration of blood to the right heart acts eventually in the reverse direction, and that on expiration the increased intrathoracic pressure forces blood from the lung to the left heart and so raises the pressure temporarily, the later fall being caused by the increased resistance in the pulmonary circuit and by the interference with venous return to the right heart and the resulting decreased supply of blood to the left heart.

These factors probably operate increasingly under the abnormal condition of pulmonary collapse and high intrapleural pressure. They might have been accepted as the sole explanation had not Fredericq⁵

4. Tigerstedt, R.: *Die Physiologie des Kreislaufes*, ed. 3, Berlin, W. de Gruyter & Co., 1923, p. 1.

5. Fredericq, cited by Tigerstedt.⁴

shown that the changes in blood pressure synchronous with respiration are independent of mechanical factors, persisting in the curarized animal with both pleural cavities widely opened. This suggested that they are caused by changes in the tone of the vasoconstrictor center produced by rhythmic variations in the oxygen and carbon dioxide content of the blood. Against this explanation is the work of Plumier,⁶ who found that the waves disappear after section of the nerves at the root of the lung.

In the normal human being the waves are not ordinarily observable. Frost,⁷ however, has shown that on deep inspiration that is held the pressure first rises a little, then falls abruptly and then rises and that on deep expiration these effects are reversed. Their noted increase in cases of increased pressure in the pleural cavity may be the result of mechanical factors, of poor aeration of the blood and of resulting changes in vasoconstriction, or of reflexes arising in the lung and acting on the vasoconstrictor center. It is my feeling that in this condition the former factors are of chief importance, namely, the great hindrance to the return of blood to the right heart and the marked changes in resistance in the pulmonary circuit.

There have been numerous clinical studies on the effect of artificial pneumothorax on the blood pressure, and both the results within the different series and the results of the different observers have been inconstant. In some patients there is a temporary rise in blood pressure, in others a fall and in others no change. Practically all investigators have agreed that with the pressures used the changes are unimportant and transitory, disappearing in the course of an hour or two. Steidl and Heise⁸ in most patients found a fall of systolic pressure of from 7 to 40 mm. of mercury as a result of simply passing the needle through the pleura. After injections of air Burstein⁹ found an average rise of pressure of 12.4 mm. of mercury. Bendove¹⁰ found an increase of pressure in eight of fourteen cases, no change in four and a fall in two. All the readings returned to normal in an hour. Vazzoler¹¹ found a constant decrease in the pulse pressure caused chiefly by a rise of from

6. Plumier, cited by Tigerstedt.⁴

7. Frost, H. M., in *New England Mutual Life Insurance Company: Life-Insurance Medicine*, Boston, 1926, vol. 1, p. 136.

8. Steidl, J., and Heise, F. H.: *The Pulse-Rate and Blood-Pressure During Artificial-Pneumothorax Insufflations*, *Am. Rev. Tuberc.* **26**:730, 1932.

9. Burstein, M. A.: *Der Einfluss des künstlichen Pneumothorax auf den Blutdruck bei Tuberkulösen*, *Ztschr. f. Tuberk.* **21**:138, 1913-1914.

10. Bendove, R. A.: *The Circulatory Changes in Artificial Pneumothorax*, *Am. Rev. Tuberc.* **12**:107, 1925.

11. Vazzoler, G.: *Di alcuni effetti sul circolo del pneumotorace terapeutico*, *Folia med.* **14**:502, 1928.

5 to 15 mm. of mercury in the diastolic level. Klukowski¹² found that it fell in 78 per cent, was unchanged in 14 per cent and rose in 8 per cent. The pulse rate was slowed in 65 per cent, unchanged in 13 per cent and increased in 22 per cent.

Bruns,¹³ Weil and Sackur,¹⁴ Rist and Carpi,¹⁵ Bernard and Robert¹⁶ and Parisot and Hermann¹⁷ agreed that in experimental animals artificial pneumothorax as used clinically causes no important or lasting change in the blood pressure. Parisot and Hermann noted a slowing of the pulse, which has also been observed by Sauerbruch¹⁸ and Walther,¹⁹ the latter having found that it does not occur if the vagus nerves are cut.

Knoll,²⁰ Rosenbach, Lieven,³ Walther, Dunn²¹ and others have studied experimentally the effects of higher pressures in the pleural cavity. Knoll found that there was no change in the blood pressure if the pressure in the pleural cavity or pericardium was raised gradually to atmospheric pressure. If it was raised rapidly above that level, there occurred first a rise in blood pressure and then an abrupt fall, which, unless the pressure was relieved, led rapidly to death. As the pressure was raised, the systemic veins became progressively engorged. After decompression the blood pressure rose far above normal, and that was interpreted as being caused by the sudden release of the intrathoracic dam and the flooding in of the blood held back in the veins.

Rosenbach, Lieven and Walther made similar observations. All of them interpreted the primary rise in blood pressure as being due to a compensating vasoconstriction. The fall in blood pressure came just before death and was abrupt. They expressed the opinion that the fall was caused by interference with the return of the venous blood by pressure on the great veins and on the right heart. Walther and Sauer-

12. Klukowski, J.: L'influence du pneumothorax artificiel sur la tension artérielle, *J. de méd. et chir. prat.* **103**:331, 1932.

13. Bruns, O.: Ueber Folgezustände des einseitigen Pneumothorax, *Beitr. z. Klin. d. Tuberk.* **12**:1, 1909; Ueber die praktische Bedeutung der Zirkulationsänderung durch einseitigen Lungenkollaps bei therapeutischen Eingriffen an der Lunge, *ibid.* **29**:253, 1913.

14. Weil and Sackur, cited by Steidl and Heise.⁸

15. Rist and Carpi, cited by Steidl and Heise.⁸

16. Bernard and Robert, cited by Steidl and Heise.⁸

17. Parisot, J., and Hermann, H.: Action sur l'appareil cardiovasculaire du pneumothorax artificiel experimental, *Compt. rend. Soc. de biol.* **135**:1034, 1922.

18. Sauerbruch, E. F.: *Die Chirurgie der Brustorgane*, ed. 2, Berlin, Julius Springer, 1920, vol. 1, p. 608; vol. 2, p. 718.

19. Walther, H. S.: *Deutsches Arch. f. klin. Med.* **119**:253, 1912.

20. Knoll: *Schmidt's Jahrb.* **146**:179, 1882.

21. Dunn, J. S.: The Effect of Experimental Pleural Effusion on the Blood Pressure in the Right Ventricle, *Quart. J. Med.* **13**:57, 1919.

bruch stressed the initial slowing of the pulse caused by stimulation of the vagus nerve. Rosenbach was the only one who noted or reported an increase in the Traube-Hering waves.

The effects of increased pressure in the pericardium bear a direct relation to the present problem. It has been frequently shown that those effects are caused purely by interference with the return of venous blood. In experiments performed in 1923 Claude Beck and I found a marked rise in the venous pressure. There was an initial rise in the blood pressure, but as the venous pressure reached a maximum and the intrapericardial pressure approached it, the blood pressure began to fall. The fall was gradual, not abrupt and rapidly fatal, as in cases of high pressure in the pleural cavity; and it could be maintained at any desired level by regulating the pressure in the pericardium. Section of the vagus nerves and avulsion of the stellate ganglions did not alter the picture. Beck and Isaac²² reported a decrease in the output of the heart which was not reflected in the blood pressure until it had become extreme.

When the pressure in the pleural cavity is raised, there are the same factors to be considered, but the condition is much less simple. There is also collapse of one lung and partial collapse of the other. There is displacement of the heart and mediastinum, a reduction in the vital capacity and a change in the blood flow through the lungs and in the pressure in the pulmonary circulation. All of those factors must be considered as contributing to the syndrome.

The older clinicians, Trousseau,²³ Bartels,²⁴ Leichtenstern,²⁵ Rosenbach and others, expressed the opinion that cardiac failure in cases of massive pleural effusion is purely a matter of displacement of the heart and torsion of the great vessels. Bartels in particular was responsible for the idea that kinking and occlusions of the vena cava account for the sudden death that occasionally occurs. That theory was upset by the demonstration at postmortem examination that those deaths are caused by embolism of the pulmonary artery, the thrombi having formed in the right auricle and ventricle. Extreme displacement of the heart by pulmonary fibrosis occasionally causes tachycardia and dyspnea, but is usually well tolerated; the simple displacement is probably a minor factor. Bruns, and Dock and Harrison²⁶ have shown that there is a

22. Beck, Claude, and Isaac, L.: Pneumocardiac Tamponade, *J. Thoracic Surg.* **1**:124, 1931.

23. Trousseau, cited by Sauerbruch.¹⁸

24. Bartels, cited by Sauerbruch.¹⁸

25. Leichtenstern, O., in Gerhardts, C.: *Lehrbuch der Kinderkrankheiten*, ed. 5, Tübingen, H. Laupp, 1897-1899.

26. Dock, W., and Harrison, T. R.: The Blood Flow Through the Lungs in Experimental Pneumothorax, *Am. Rev. Tuberc.* **10**:534, 1925.

decreased flow of blood through a collapsed lung. Richards, Riley and Hiscock²⁷ found an appreciable reduction in the output of the heart during artificial pneumothorax. With high pressures Dunn observed a rise in pressure in the right ventricle, and it has been noted that it falls abruptly shortly before the fall in systemic pressure. Schlaepfer²⁸ found that ligating one pulmonary artery causes a rise in pressure in the opposite artery, and Horine and Warner²⁸ have recently shown that ligation of one pulmonary artery causes a transient fall in the systemic pressure, which disappears in thirty seconds, but if the vasomotor center is thrown out by section of the cervical portion of the spinal cord, the pressure continues to fall, and the dog dies. Bendove noted an increase in the pulmonary second sound and in the transverse diameter of the heart in patients who responded to artificial pneumothorax with a rise in blood pressure.

CONCLUSION

It can be said, therefore, that high pressure in the pleural cavity acts directly on both the pulmonary and the systemic circulation: on the former by collapsing the lung and on the latter by compressing the great veins.

Collapse of the lung causes: (1) a decrease in the flow of blood through the collapsed lung, (2) a rise in pressure in the pulmonary circulation, (3) an increased strain on the right heart and (4) a reduction in the vital capacity.

Compression of the great veins causes: (1) a rise in the venous pressure, (2) an insufficiency in the return of venous blood and (3) a decreased output of the heart.

Up to relatively extreme degrees of pressure these hindrances are compensated for by an increase in tone of the vasoconstrictor center. The first sign of the strain on this compensatory mechanism is an exaggeration of the Traube-Hering waves, a tendency for the peripheral resistance to give way during inspiration. A time comes when the center can no longer fully compensate, and the mean blood pressure falls below the critical level.

27. Richards, D. W., Jr.; Riley, C. B., and Hiscock, M.: Cardiac Output Following Artificial Pneumothorax in Man, *Arch. Int. Med.* **49**:994 (June) 1932.

28. Schlaepfer, cited by Horine, C. F., and Warner, C. G.: Experimental Occlusion of the Pulmonary Artery: Anatomic Study, *Arch. Surg.* **28**:139 (Jan.) 1934.

ACUTE GLOMERULONEPHRITIS FOLLOWING PNEUMOCOCCIC LOBAR PNEUMONIA

ANALYSIS OF SEVEN CASES

DAVID SEEGAL, M.D.

NEW YORK

Twenty years ago Volhard and Fahr¹ stated that the streptococcus played the most important rôle in the various types of nephritis and that the pneumococcus was the next most important infectious agent. Rake² recently reviewed the literature concerning the importance of the pneumococcus in the etiology of nephritis and called attention to the fact that whereas the streptococcus has recently received the chief attention, numerous papers appearing in the last decade of the nineteenth century dealt with the significance of pneumococcic infection as an inciting agent in acute nephritis. The recent comprehensive clinical and experimental studies of Blackman and his associates³ produced renewed interest in the problem. These authors noted pathologic evidence of acute nephritis in 9.4 per cent of 95 young children who died of the various types of pneumococcic infection. "Outspoken examples of acute nephritis were found only in infants with pneumococcal infections, usually of long duration, other than pneumonia alone. It was not present in the kidneys of the adults studied who had similar, chronic pneumococcal infection."

This study consists of a clinical analysis of 7 cases of acute glomerulonephritis following pneumococcic lobar pneumonia which occurred in 1,004 instances of the latter condition seen at the Presbyterian Hospital between 1918 and 1933. All the cases were diagnosed clinically. Postmortem studies were not made on the 2 patients who died.

Only the cases diagnosed as instances of pneumococcic lobar pneumonia and acute nephritis were included in this report. It is believed that a number of cases of acute nephritis following lobar pneumonia were overlooked, since the failure to carry out comprehensive laboratory studies may have prevented the diagnosis of this disease. Three cases of acute nephritis following lobar pneumonia in which typing

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.

1. Volhard, F., and Fahr, K. T.: *Die Brightsche Nierenkrankheit*, Berlin, Julius Springer, 1914.

2. Rake, G.: *Guy's Hosp. Rep.* **83**:430, 1933.

3. (a) Blackman, S. S.; Brown, J. H., and Rake, G.: *Bull. Johns Hopkins Hosp.* **48**:74, 1931. (b) Blackman, S. S., and Rake, G.: *ibid.* **51**:217, 1932. (c) Blackman, S. S.: *ibid.* **55**:1, 1934; (d) *ibid.* **55**:85, 1934.

of the sputum was unsatisfactory were excluded from this study. Two cases of acute glomerulonephritis in children which seemed to be associated with pneumococcic infection were eliminated from the series because of inadequate laboratory studies.

ANALYSIS OF CASES

The table presents in outline the analysis of the histories of the 7 patients with acute glomerulonephritis associated with pneumococcic lobar pneumonia. The following data were selected for study:

Age.—One patient was in the second decade of life, 2 in the third, 3 in the fourth and 1 in the fifth.

Sex.—Five of the patients were men, and 2 were women. In a study⁴ of 381 cases of acute glomerulonephritis in which the chief preexisting infectious agent was the hemolytic streptococcus, it was found that the disease developed twice as frequently in men as in women.

Past History of Nephritis.—None of the 7 patients gave a past history of symptoms or signs indicative of preexisting nephritis.

Culture of the Sputum.—The cultures obtained from the sputum showed pneumococcus type I in 4 patients, pneumococcus type II in 1 and pneumococcus type III in 2.

Culture of the Blood.—In 5 of the patients the blood culture was negative throughout the course of the pneumonia. In 1 of the patients who died a type I pneumococcus was revealed in the blood on three occasions early in the course of the pneumonia. After specific serum therapy the blood culture became negative. In the second patient a type III pneumococcus was observed repeatedly in the blood before death. No cardiac murmurs or embolic phenomena were noted in this patient.

Complications.—Three of the patients had no complications. One of the patients presented the signs of mitral stenosis without evidence of active rheumatic fever or cardiac insufficiency. In 1 case serum disease appeared. In another instance of serum disease otitis media and mastoiditis were found to be caused by the pneumococcus. Pericarditis was the complication in the seventh case.

Interval in Days Between the Onset of Pneumonia and the Probable Onset of Nephritis.—While it was possible to determine with reasonable accuracy the day of onset of the pneumonia, it was difficult to judge the exact day of onset of the acute nephritis, since urinalyses were made as a routine only at weekly intervals and the problem of renal complication was not generally considered by the attending physician until the appearance of a dramatic sign or symptom of the disease.

4. Seegal, D.; Seegal, B. C., and Lyttle, J. D.: Unpublished observations.

Analysis of Seven Cases of Acute Glomerulonephritis

Name	Age, Years	Sex	Past History of Nephritis	Pneumococcus in Culture of the Sputum	Blood Culture	Complications	Interval Between Onset of Pneumonia and Probable Onset of Nephritis, Days	Examination of Urine During Pneumonia and Prior to Probable Onset of Nephritis		Examination of Urine After Onset of Nephritis	
								Albumin	Sediment	Albumin	Sediment
C. D.	24	M	Negative	Type II	Negative	None	± 20	VFT VFT VFT	Negative Negative Negative	VHT	Few red cells; many hyaline and granular casts; few cellular casts
J. H.	38	M	Negative	Type I	Negative	None except serum disease	± 20	FT FT T	Negative Negative Negative	HT	Many hyaline and granular casts; many red cells
J. F.	35	M	Negative	Type III	Positive 3 times during course	Pericarditis	± 21		No data	HT	Many casts; many red cells
A. S.	28	F	Negative	Type I	Positive 3 times early in course	Otitis media due to pneumococcus type 1; mastoiditis due to pneumococcus type I; serum disease	± 16	FT VFT FT	Occasional red cells (patient menstruating) Negative Negative	HT	Occasional cellular casts; many red cells
T. L.	49	M	Negative	Type I	Negative	None	± 21	FT FT VFT None	Many granular casts Occasional white blood cells Moderate number of white cells Few casts	T	Many casts of all kinds; many red cells
J. L.	16	M	Negative	Type I	Negative	None	± 14	FT T T	Negative Negative Few casts	HT	Many casts; urine loaded with red cells, smoky
G. R.	38	F	Negative	Type III	Negative	None except inactive rheumatic cardiac disease with mitral stenosis	± 19	FT FT FT	Negative Negative Negative	HT	Many casts; many red cells

* VFT indicates a very faint trace of albumin; FT, a faint trace; T, a trace; VHT, a very heavy trace; and HT, a heavy trace.

*Following Pneumococcic Lobar Pneumonia **

Blood Urea, Mg.	Phenol-sulphon-phthalin Test, Percent- age Excreted	Blood Pressure		Examina- tion of Eye- grounds	Edema	Decrease in Red Cell Count During Nephritis	Treat- ment with Speci- fic Serums	Serum Sick- ness	Comment
		Sys- tolic	Dias- tolic						
4.34	15	105	48	Few	Mod-	2,500,000	Not	None	Patient followed in outpatient department for 2 months, during which he continued to show a heavy trace of albumin and normal blood pressure; no further observations
2.82	49	120	58	fresh	erate		given		
0.62	56			hemor-					
0.29				rhages					
0.53	42	120	80	Normal	None	1,200,000	Given	Pres-	No data available after discharge
0.35								ent	
1.13	No test	130	70	Normal	None	No data	Not	None	Previous attack of pneumonia 1 month before present bout; patient well for 10 days, when second attack occurred, which led to death
1.27	made						given		
2.51	45 early	102	65	Not	Marked	1,800,000	Given	Pres-	Patient died of uremia 1 month after onset of nephritis; 1 culture made from throat showed hemolytic Staph. aureus
2.98	in course	116	66	made				ent	
2.66	of nephri-	125	75						
2.70	tis	140	70						
3.10									
3.50									
1.28	15 early;	130	65	Not	Slight	1,600,000	Not	None	Healing in 1 year, when blood pressure was 116 systolic and 75 diastolic and 140 systolic and 80 diastolic, and urinalysis twice gave negative results; scarlet fever without complications in childhood
	50 at dis-	155	90	made			given		
	charge	100	60						
	from								
	hospital								
1.60	50	110	65	Normal	None	1,400,000	Not	None	Healing in 14 months; repeated negative results of urinalyses for next 9 years
1.20	30	130	90				given		
0.26	35								
	25								
	30								
	40								
	50								
	60								
	65								
1.31	52	96	70	Normal	None	1,200,000	Not	None	Healing in 7 months
0.89		100	50				given		
0.52		116	64						
0.27		115	78						
		120	80						

Nevertheless, it was possible to gain an approximate idea of the day of onset of nephritis. The table shows that an interval of from fourteen to twenty-one days intervened between the onset of pneumonia and that of acute nephritis. In 4 of the cases there was an afebrile period of three, four, six and seven days, respectively, prior to the recognized onset of renal inflammation. It appears that the "silent period" observed in cases of postscarlatinal nephritis is also present in this group of cases of nephritis after pneumococcic lobar pneumonia.

Examination of the Urine During Pneumonia and Prior to the Probable Onset of Nephritis.—The table shows that urinalyses during pneumonia and prior to the probable onset of nephritis revealed small amounts of albumin and nothing of significance in the sediment, except in one or two determinations in which casts were observed. Gross hematuria and microscopic evidence of red cells in the sediment were not noted except in the case of A. S., who was menstruating at the time of admission. Two of the subsequent urinalyses in this case prior to the onset of nephritis showed nothing of significance in the sediment.

Examination of the Urine After the Onset of Nephritis.—Urinalyses at the onset of nephritis gave characteristic results, and hematuria was a dominant feature. Albuminuria was marked, and all the types of casts usually associated with the diagnosis of acute nephritis were repeatedly observed. Neale⁵ analyzed the results of urinalysis in 287 cases of lobar pneumonia in adults and noted that in 3.4 per cent albuminuria, cylindruria and microscopic hematuria were shown between the third and the tenth day after the onset of the disease.

Blood Urea.—Retention of nitrogen occurred in all 7 cases.

Phenolsulphonphthalein Test.—Three of the patients showed marked diminution in their ability to excrete phenolsulphonphthalein during the early stages of nephritis, but in all these persons the results of the phenolsulphonphthalein test were normal on the patient's discharge from the hospital. All the remaining patients on whom the test was performed showed no evidence of retention of the dye.

Blood Pressure.—A striking feature in this series of cases was the absence of significant hypertension, particularly in the diastolic phase. None of the patients showed a diastolic blood pressure of over 90, and in 5 of the 7 cases the diastolic blood pressure never exceeded 80. One patient, aged 49, had a systolic blood pressure of 155 on one occasion. The two other readings in this case were 130 and 100. Another patient had a systolic blood pressure of 140, but three other readings were 102, 110 and 125. With these two exceptions, the systolic blood pressure was never found to exceed 130.

5. Neale, A. V.: Brit. M. J. 2:891 (Nov. 17) 1928.

It was surprising to find such a striking absence of hypertension in a group of 7 patients with acute nephritis, in whom the results of urinalysis and the values for blood urea were so abnormal.

Examination of the Eyegrounds.—Examination of the eyegrounds was made in 5 of the 7 cases. No findings were revealed indicative of preexisting damage. In one case a few fresh hemorrhages observed during the acute stage of the nephritis disappeared later.

Edema.—In 4 of the patients demonstrable subcutaneous edema failed to develop. In 1 case there was slight, in a second moderate, and in a third marked, edema.

Decrease in Red Blood Cell Count During the Nephritis.—In the 6 patients for whom adequate data were available, the decrease in the red blood cell count during the course of the nephritis was striking. The table shows that the highest reduction in the count was 2,500,000 and the lowest 1,200,000.

Treatment with Specific Serums.—Two of the patients with type I pneumococcic infection received antipneumococcus horse serum. Serum sickness developed in both, and 1 patient died of uremia. The nephritis which occurred in these cases could not be confused with the renal changes of serum sickness which have been described by Rackemann, Longcope and Peters.⁶

Course of the Nephritis.—In 1 of the 2 patients who died terminal uremia developed one month after the onset of nephritis. The cause of the death of the second patient was considered to be pneumococcic septicemia complicated by pericarditis. There was no clinical evidence of bacterial endocarditis. The nephritis was not considered the cause of death but may have contributed to it. Three of the patients were carefully observed subsequently and the lesions were considered healed in from seven to fourteen months after the onset of renal inflammation. The sixth patient was observed for two months and continued to show severe albuminuria and a normal blood pressure. His further history is unknown. The seventh patient could not be adequately studied after his discharge.

COMMENT

Analysis of the histories in the 7 cases included in this study shows that a typical picture of acute glomerulonephritis followed pneumococcic lobar pneumonia. The clinical features characteristic of the nephritis are outlined in the table. The histories in these cases in adults may be offered as further evidence that the pneumococcus or its products are

6. Rackemann, F. M.; Longcope, W. T., and Peters, J. P.: The Excretion of Chlorids and Water and the Renal Function in Serum Disease, Arch. Int. Med. 18:496 (Oct.) 1916.

capable of inducing acute glomerulonephritis. This group of cases may be classified with those of infants with clinical histories of acute nephritis following pneumococcic infection which were described by Blackman and Rake.^{3b}

The histories of the 7 patients and the data obtained from laboratory examinations were carefully studied to determine the presence of infections other than those caused by the pneumococcus. Such concomitant infections were absent. In 1 case a culture made as a routine of material from a normal-appearing throat showed hemolytic *Staphylococcus aureus* but no hemolytic streptococcus. In a second case, that of a patient who never manifested symptoms or signs of pharyngitis, cultures of material from the throat made on the second and on the eighteenth day of the nephritis showed no hemolytic streptococcus. On the thirtieth day, when the nephritis was subsiding, a culture of material from the throat showed alpha prime (not beta) hemolytic streptococcus. Results of determinations of antistreptolysin made on the serum of this patient were within normal limits. Similar determinations carried out on the serum of another patient with nephritis following lobar pneumonia also gave normal values. The last-mentioned case has been excluded from this series, since the typing of the sputum was unsatisfactory. Studies⁷ of the antistreptolysin titer of patients with acute nephritis following infection with the hemolytic streptococcus showed values higher than normal in the great majority of the cases. Although it is impossible to exclude the possibility of a concomitant infection due to the hemolytic streptococcus in these cases of lobar pneumonia which were followed by acute glomerulonephritis, the accurate clinical observations lend little credence to this possibility.

During the period in which this series of cases was studied there were 1,004 cases of pneumococcic lobar pneumonia at the Presbyterian Hospital. The incidence of acute nephritis following lobar pneumonia at this hospital is, therefore, about 0.7 per cent. This value would probably be higher if opportunity had been available to study all the cases of lobar pneumonia more carefully.

The incidence of nephritis following scarlet fever is considered to be in the neighborhood of from 1 to 2 per cent. Recently, Lucchesi and Bowman⁸ found nephritis a complication in only 1.26 per cent of 5,377 cases of scarlet fever. It is surprising to note how closely the frequency for nephritis following pneumococcic lobar pneumonia approaches this value. Since the total number of infections due to the hemolytic streptococcus in New York City is far greater than the

7. Seegal, D., and Lyttle, J. D.: *Proc. Soc. Exper. Biol. & Med.* **31**:211, 1933; unpublished observations.

8. Lucchesi, P. F., and Bowman, J. E.: *Antitoxins Versus No Antitoxin in Scarlet Fever*, *J. A. M. A.* **103**:1049 (Oct. 6) 1934.

number due to the pneumococcic infections, it seems only reasonable to assume that in the great majority of cases acute nephritis is due to the former organism.

CONCLUSIONS

An analysis has been made of the histories of 7 patients with acute glomerulonephritis following pneumococcic lobar pneumonia.

The nature of the data obtained from the laboratory and certain points in the clinical history have been shown in tabular form and commented on.

The nephritis develops in from two to three weeks after the onset of the pneumonia and is characterized by severe albuminuria, hematuria, moderate to marked retention of nitrogen, striking reduction in the red cell count, slight to marked edema in one-half the cases and absence of significant hypertension.

Evidence of a concomitant infection due to the hemolytic streptococcus is not found in the clinical history.

The incidence of acute glomerulonephritis following pneumococcic lobar pneumonia in 1,004 cases was 0.7 per cent. This value closely approximates that for the incidence of nephritis following scarlet fever.

RELATIONSHIP OF PELLAGROUS DERMATITIS TO SUNLIGHT

TOM D. SPIES, M.D.

CLEVELAND

In the early descriptions observers expressed the belief that pellagra was caused by the sun, and it was accordingly designated by many writers as *mal de la sol* or sickness of the sun.¹ Since that time various writers have held that sunlight was either the sole cause or a major factor in the pathogenesis of the disease. Bass,² Ormsby,³ Sutton⁴ and Ruffin and Smith⁵ described the development of pellagrous erythema in pellagrins exposed to direct sunlight. Some writers believed that the pellagra-producing portion of the sunlight is present in the violet end of the spectrum.⁶ All these conclusions have, of necessity, been based on personal interpretations, at times without full regard for the inherent difficulties in distinguishing between the erythema of sunburn and that of pellagra.

The present study is concerned with observations on pellagrous dermatitis and the relationship of these cutaneous changes to exposure to sunlight.

METHODS AND OBSERVATIONS

During the past three and a half years thirty patients with pellagra and two normal persons were studied at the Lakeside Hospital in the following manner:

1. Ten pellagrins were exposed to large doses of ultraviolet radiation at a distance of 20 inches (53.34 cm.) while they were restricted to a diet of 2,900 calories, low in the pellagra-preventive substances. Each of the ten patients received daily increasing doses of radiation from a quartz mercury vapor arc lamp

From the H. K. Cushing Laboratory of Experimental Medicine, Department of Medicine, Western Reserve University, and the Medical Service, Lakeside Hospital.

1. Roberts, S. R.: Pellagra, St. Louis, C. V. Mosby Company, 1912, p. 133.

2. Bass, C. C., quoted by Roberts.¹

3. Ormsby, O. S.: A Practical Treatise on Diseases of the Skin, ed. 4, Philadelphia, Lea & Febiger, 1934, p. 417.

4. Sutton, R. L.: Diseases of the Skin, ed. 8, St. Louis, C. V. Mosby Company, 1931, p. 171.

5. Ruffin, J. M., and Smith, D. T.: The Treatment of Pellagra with Certain Preparations of Liver, Am. J. M. Sc. **187**:512, 1934.

6. Roberts,¹ p. 134.

for a period from four to forty minutes over a characteristic pellagrous lesion and also over another area of normal-appearing skin. In every instance the corresponding anatomic area on the opposite side of the body was protected from irradiation and served as a control.

The patch of normal-appearing skin of the ten pellagrins became increasingly pigmented after irradiation, but the area was not unlike the similarly exposed skin of the normal subjects. In no instance could the induced pigmentary changes be diagnosed as pellagrous, although the irradiated areas were well demarcated and passed through the stages of erythema, darkening and desquamation. Likewise, exposure of the pellagrous lesions to ultraviolet radiation was followed by additional pigmentary change, but irradiation did not prevent the dermatitis from healing.



Fig. 1.—Increased pigmentation of the antecubital fossa of a normal person and of a pellagrin after identical exposure to sunlight. The areas may be compared with the area of pellagrous dermatitis on the wrist of the pellagrin.

2. In eight other patients on the same diet low in pellagra-protective substances the area of pellagrous dermatitis was exposed to direct sunlight in increasing doses, ranging from twenty to sixty minutes each day, for a period of from seven to twenty days. In six of the eight patients also areas of normal-appearing skin were exposed to sunlight for the same intervals of time. In all the patients ipsilateral portions of the body were protected from sunlight.

The exposed areas of normal-appearing skin reddened at first, often became swollen and later desquamated and became pigmented, but none of them could be diagnosed as pellagrous. The exposure of the pellagrous lesion itself to sunlight was followed by somewhat similar changes, but the exposure did not prevent healing of the underlying pellagrous dermatitis.

3. In order to compare the effects of sunlight on the normal-appearing skin of pellagrins and on the skin of normal persons, two pellagrins and two normal persons with a similar degree of pigmentation were exposed to the sun in an identical manner. During the study the normal subjects received a generous diet high in calories and in nutritive value, and the pellagrins were restricted to one low in pellagra-preventive substances. Each person was exposed for one hour each day for five consecutive days.

The exposed skin of the normal subjects and of the pellagrins became reddened and swollen with subsequent desquamation (fig. 1), but little if any evidence could

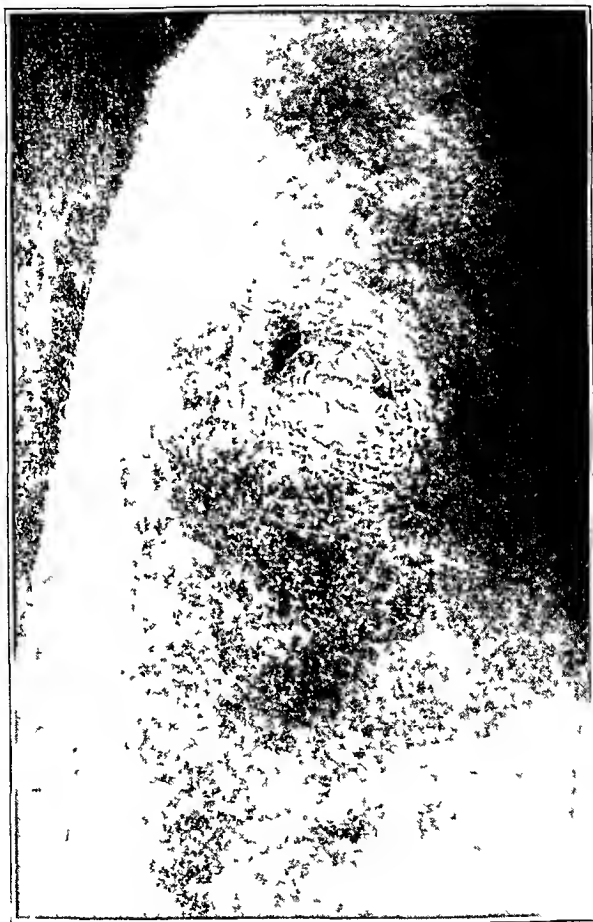


Fig. 2.—A well demarcated lesion of pellagrous dermatitis which developed in the absence of direct sunlight.

be obtained of difference in the intensity or character of the response of the skin.

No pellagrin in the studies just outlined had a general relapse of the disease. Each patient ingested the full 2,900 calorie allowance of food and did not show additional signs or symptoms of pellagra, such as glossitis, dermatitis, stomatitis, diarrhea, vomiting or psychic changes.

4 To determine whether or not in potential pellagrins dermal changes could develop in the absence of direct sunlight, four adult volunteers, who had had numerous previous attacks of pellagra but were free from lesions at the time, were

offered a deficient diet. They were not urged to eat the food, however, since it was thought that they would eat less and less and that the disease would soon develop. Each patient was given 20 cc. of castor oil three times a day with the hope that excessive purgation might also aid in producing the disease. These volunteers were kept in the hospital away from direct sunlight throughout the course of the experiment.



Fig. 3.—Bilaterally placed, well demarcated areas of pellagrous dermatitis which appeared without exposure to direct sunlight.

Each patient ate less and less and consequently lost considerable weight by the end of the first month. Within six weeks each subject displayed distaste for the diet and definite changes of pellagra, characterized by dermatitis (figs. 2 and 3) and mild redness of the tongue and mouth; two of the patients began to vomit. When the diet was changed to an adequate one, they quickly improved.

COMMENT

It must be admitted that clinicians cannot always distinguish between sunburn in normal persons and the erythematous lesions of pellagra, with the result that the diagnosis of pellagra is often made only by means of the history with little or no consideration for the fact that in a person receiving either an inadequate diet or a normal one sunburn might develop in a similar manner. At present there is a tendency to diagnose as pellagrous all symmetrically distributed cutaneous lesions on the hands of persons existing on a poor diet. Prolonged exposure to sunlight is toxic in varying degrees to normal persons, and it is recognized that sunlight in general augments the severity of certain diseases of the skin. In the clinic with which I am associated, where alcoholism predisposes to dietary insufficiency, pellagra occurs throughout the winter months. In the South, where there is a definite increase in the frequency of pellagra in the spring, the incidence of the disease is decidedly less during July and August, when there is certainly no decrease in sunshine. Moreover, pellagra develops in Negroes, who are naturally somewhat protected from sunlight by the pigment of the skin.

Many writers maintain that the dermatitis of pellagra occurs only on the exposed surfaces, but that is not true of patients in this clinic, for the feet, perineal region, elbows and other parts of the body are frequently involved. This study has demonstrated that pellagrous lesions of the skin may develop in the absence of sunlight and that exposure of areas of pellagrous dermatitis either to large doses of ultraviolet radiation or to direct sunlight does not prevent healing of the lesions, even when the patient is limited to a pellagra-producing diet. (All these patients took the full diet of 2,900 calories, low in pellagra-preventive substances, each day.) These observations, however, do not prove that sunlight may not exert an irritating effect, and they certainly do not eliminate the possibility that exposure to sunlight may precipitate the early lesions of the skin. According to the studies carried on in this clinic, the dermatitis of pellagra never remains static; it either improves or becomes worse, thus making controlled experimentation of a quantitative nature for a period of time almost impossible.

Recently, Ruffin and Smith studied pellagrous dermatitis and reported that the exposure to sunlight of some pellagrins on a pellagra-producing diet causes the appearance of the dermal changes of the disease in the exposed area. Even if one accepts it as fact that the induced cutaneous changes in their cases were pellagrous and not due to sunburn, it is impossible to state that the relationship between exposure to sunlight and the development of pellagrous dermatitis is definitely one of cause and effect. The histories in two of their cases clearly showed

that oral lesions of pellagra and diarrhea developed simultaneously with the appearance of dermatitis at the area of exposure. Should not one conclude, then, that if sunlight produced the dermatitis it caused the stomatitis, glossitis and diarrhea too? It is possible that the patients may have had a general relapse, which often occurs in this disease.

Since so many observers during the past two hundred years have believed that the lesions of pellagra are caused by sunlight, serious consideration should be given to the possibility of a relationship between them. On purely theoretical grounds it seems probable either that the sun acts as an irritant, its heat hastening the cutaneous eruption, or that it effects a specific chemical change which in turn produces dermatitis. Since my studies have shown that the dermal changes of pellagra can be induced in the absence of sunlight and since the pellagrous changes of the skin are often observed over the points liable to irritation, such as the hands, elbows, axillae, skin under the breasts, feet, sacrum and perineum, it seems reasonable to suggest that sufficient irritation of any kind might predispose the area to localization of the dermatitis. The sun in North Carolina, where the studies of Ruffin and Smith were carried out, gives more direct rays which are less filtered by smoke than in Cleveland, where my studies were made. For this reason, it is impossible to state that the characteristic dermatitis of pellagra cannot be produced at times by sunlight in the manner described by these investigators. From a practical standpoint, however, it should be borne in mind that the disappearance of dermatitis does not necessarily mean the cure of pellagra. The other manifestations of the disease often exist without involvement of the skin and may even cause the death of the patient without reappearance of the dermatitis.

Although pellagra received its name because of its rather characteristic cutaneous lesions, it should not be considered purely a disease of the skin any more than syphilis or smallpox, both of which have changes in the skin of diagnostic value. Since cutaneous manifestations are common to many systemic conditions, the finding of them in pellagra by analogy should not be surprising and should lead to their interpretation as a local reaction to a systemic disease of diagnostic importance. There is no entirely satisfactory explanation at this time as to why the skin should or should not be involved in pellagra, but if the fact is accepted that measles is likely to begin on the face, scarlet fever on the body and typhoid fever with rose spots on the abdomen, it does not seem too novel to suggest that pellagra has a predilection for the hands, face, feet, knees, perineum and other sites. The affinity of various diseases for certain organs and locations is still inexplicable.

SUMMARY AND CONCLUSIONS

It has been shown in the present study that pellagrous lesions occur in the absence of sunlight and that they may heal in the presence of exposure to direct sunlight or to ultraviolet radiation.

It is suggested that pellagra should be considered not as a disease of the skin but as a systemic condition which in itself is the real cause of pellagrous dermatitis rather than any incidental or experimental exposure to the rays of the sun.

It is pointed out that under certain conditions sunlight may act as an irritant and precipitate the cutaneous lesions; but this at present is still a matter of conjecture.

INTERPRETATION OF ABNORMAL DEXTROSE TOLERANCE CURVES OCCURRING IN TOXEMIA IN TERMS OF LIVER FUNCTION

S. SOSKIN, M.D.

M. D. ALLWEISS, M.D.

AND

I. A. MIRSKY, M.D.

CHICAGO

The decreased tolerance for carbohydrate which occurs in patients with acute infectious diseases has been confirmed recently by Williams and Dick,¹ whose paper contains an excellent review of the previous literature. A similar disturbance in carbohydrate metabolism has been demonstrated in experimentally induced toxemias in animals.² The "diabetic" type of dextrose tolerance curve obtained in the conditions mentioned has been interpreted by some as being due to a lack of endogenous insulin, consequent to the functional impairment of the islands of Langerhans.³ Others have ascribed the phenomenon to an interference with the action of the available insulin, whether of endogenous or of exogenous origin.⁴

This study was aided by the Max Pam Fund for Metabolic Research.

Presented in preliminary form before the Central Society for Clinical Research, Nov. 2, 1934.

From the Metabolic Laboratory of the Department of Physiology, Michael Reese Hospital, and the Department of Physiology, University of Chicago.

1. Williams, J. L., and Dick, G. F.: Decreased Dextrose Tolerance in Acute Infectious Diseases, *Arch. Int. Med.* **50**:801 (Dec.) 1932.

2. (a) Tisdall, F. F.; Drake, T. G. H., and Brown, A.: The Production of a Lowered Carbohydrate Tolerance in Dogs, *Am. J. Dis. Child.* **32**:854 (Dec.) 1926. (b) Sweeney, J. S., and Lackey, R. W.: The Effect of Toxemia on Tolerance for Dextrose, *Arch. Int. Med.* **41**:257 (Feb.) 1928. (c) Sweeney, J. S.: Effect of Toxemia on the Tolerance for Dextrose and on the Action of Insulin, *ibid.* **41**:420 (March) 1928. (d) Schwentker, F. F., and Noel, W. W.: The Circulatory Failure of Diphtheria: The Carbohydrate Metabolism in Diphtheria Intoxication, *Bull. Johns Hopkins Hosp.* **46**:259, 1930. (e) Lawrence, R. D., and Buckley, M. B.: The Inhibition of Insulin Action by Toxaemias and Its Explanation: I. The Effect of Diphtheria Toxin on Blood Sugar and Insulin Action in Rabbits, *Brit. J. Exper. Path.* **8**:58, 1927. (f) Sweeney, J. S.; Barshop, N., and LoBello, L. C.: Effect of Toxemia on the Tolerance for Dextrose and on the Action of Insulin, *Arch. Int. Med.* **53**:689 (May) 1934. (g) Sweeney, J. S.; Barshop, N.; LoBello, L. C., and Rosenthal, R. S.: Effect of Toxemia on the Tolerance for Dextrose and on the Action of Insulin: II. *ibid.* **54**:381 (Sept.) 1934.

3. Williams and Dick.¹ Sweeney and Lackey.^{2b} Sweeney.^{2c}

4. Lawrence and Buckley.^{2e} Sweeney, Barshop and LoBello.^{2f} Sweeney, Barshop, LoBello and Rosenthal.^{2g}

The former interpretation is based on the belief that the normal dextrose tolerance curve is dependent on an increase in the circulating insulin consequent to pancreatic stimulation by the administered dextrose. We have shown recently, however, that a normal dextrose tolerance curve may be obtained in a completely depancreatized dog which is receiving a constant injection of insulin and dextrose just sufficient to maintain the blood sugar at a constant level.⁵ An animal in this condition, moreover, shows a hypoglycemic reaction at least as great as that of a normal dog following the cessation of prolonged administration of dextrose.⁶ The absence of the pancreas precludes the possibility of an extra secretion of insulin into the blood stream following the administration of sugar. Since the normal reactions to the administration of dextrose do not require the secretion of additional insulin, it seems clear that the abnormal curves of toxemia do not result from the lack of extra secretion.

Our previous work⁵ has shown that a hepatectomized dog receiving a constant injection of dextrose just sufficient to maintain the blood sugar at a constant level yields consistently "diabetic" dextrose tolerance curves. Hence, the presence of the normal liver is essential to the normal response. From the results of simultaneous observations on the blood sugar content of the blood entering and leaving the liver during tests⁵ for dextrose tolerance, it was concluded that in the presence of a sufficiency of circulating insulin, but not necessarily of an extra secretion from the pancreas, the normal liver responds to administered dextrose by decreasing its output of blood sugar, which it previously has been supplying from its own resources. The existence of such a homeostatic mechanism of the liver as we have postulated has been confirmed substantially in a recent paper by Tsai and Yi,⁷ who calculated the quantity of sugar entering and leaving the liver by means of a flowmeter. This mechanism of the liver may be visualized more easily perhaps as being analogous to the control of temperature by a thermostatically regulated furnace. In this analogy the endocrine balance, as represented by the integrated influences of insulin and the hormones of the anterior lobe of the pituitary, the thyroid and the adrenal glands, corresponds to the factors determining the sensitivity and the threshold of the thermostat. The blood sugar level corresponds to the room temperature and is the stimulus which activates the regulatory mechanism of the liver.

5. Soskin, S.; Allweiss, M. D., and Cohen, D. J.: Influence of the Pancreas and the Liver upon the Dextrose Tolerance Curve, *Am. J. Physiol.* **109**:155, 1934.

6. Soskin, S., and Allweiss, M. D.: The Hypoglycemic Phase of the Dextrose Tolerance Curve, *Am. J. Physiol.* **110**:4, 1934.

7. Tsai, C., and Yi, C. L.: Carbohydrate Metabolism of the Liver: III. The Sugar Intake During Glucose Absorption, *Chinese J. Physiol.* **8**:273, 1934.

From the foregoing experiments it appeared probable that toxemia interferes with the homeostatic mechanism of the liver already described through its effects on the liver itself. It therefore seemed of interest to attempt to demonstrate by our methods the influence of experimentally induced toxemia on the dextrose tolerance curve in the absence of the pancreas.

METHODS

All these experiments were performed on unanesthetized normal and depancreatized dogs, which were trained to lie quietly on an animal board while the injections were given and the samples of blood taken by means of venous puncture with hypodermic needles. As in our previous work, the test sugar always was given intravenously to avoid variations due to absorption. Food and insulin were withheld for eighteen hours prior to each test. The dose of diphtheria toxin⁸ required to produce rapid onset of toxic symptoms and disturbances in carbohydrate metabolism in our animals was found, by preliminary studies, to range from 80 to 160 minimal lethal doses per kilogram of body weight, administered intravenously. Less toxin was necessary in the depancreatized dogs than in the normal dogs.

In all experiments a preliminary test for dextrose tolerance was made, at the termination of which the suitable dose of toxin was administered. One hour later a second test for dextrose tolerance was made. Control experiments in which the administered toxin was rendered inert by boiling for five minutes were also done. The procedure with the depancreatized dogs was identical with that employed on the normal dogs except that a constant blood sugar level was first established by the constant injection of dextrose plus insulin, as described in our previous articles.⁹ Once they were adjusted, the injections were continued unchanged throughout the experiment.

RESULTS

The effect of the intravenous administration of diphtheria toxin on the subsequent dextrose tolerance curve was uniformly distinct in all our experiments. Typical results are detailed in table 1 and illustrated by charts 1 and 2.

It may be seen that in normal dogs the administration of the toxin caused a definitely abnormal prolongation of the subsequent tolerance curve (table 1, fig. 1, solid lines), while the injection of boiled toxin was without effect (table 1, fig. 1, broken lines). In the depancreatized dogs (table 1, fig. 2) the administration of toxin was followed by curves even more "diabetic" than those obtained after the injection of toxin into the normal animals, although the preliminary tolerance curves were quite normal.

SUMMARY AND COMMENT

Our results show:

1. The acute toxemia resulting from the intravenous administration of adequate amounts of diphtheria toxin always brings about an

8. Eli Lilly & Co. supplied the standardized potent diphtheria toxin.

9. Soskin, Allweiss and Cohen.⁵ Soskin and Allweiss.⁶

Effect of Intravenous Administration of Diphtheria Toxin on the Subsequent Dextrose Tolerance in Normal and Depauperized Dogs

Subject	No.	First Dextrose Tolerance Test*						Diphtheria Toxin Injected Intravenously	Second Dextrose Tolerance Test*							
		Before	30 Min.	60 Min.	90 Min.	120 Min.	150 Min.		180 Min.	Before	30 Min.	60 Min.	90 Min.	120 Min.	150 Min.	180 Min.
Normal dog	1	93	312	206	85	76	...	71	160 M.L.D. per kilogram	74	322	243	171	138	102	...
	2	60	283	84	48	53	63	..	160 M.L.D. per kilogram (boiled for five minutes)	55	226	60	20	19	21	23
Depauperitized dog (blood sugar maintained at a constant level)	1	123	354	197	146	131	124	100	80 M.L.D. per kilogram	65	410	286	208	...	181	211
	2	50	193	121	96	81	62	70	80 M.L.D. per kilogram	106	297	216	222	233
	3	123	317	203	159	131	108	97	80 M.L.D. per kilogram	93	...	254	234	227	216	208

* The values are expressed in milligrams per hundred cubic centimeters of blood.

* The values are expressed in milligrams per hundred cubic centimeters of blood.

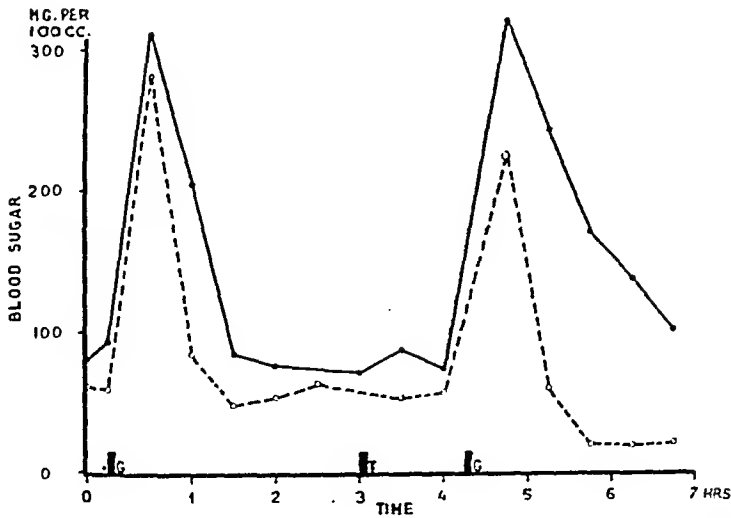


Fig. 1.—Results of tests for dextrose tolerance in normal dogs before and after the administration of toxin. In the experiment represented by the broken lines the toxin was boiled for five minutes before administration. G indicates the administration of the test sugar and T the administration of the toxin.

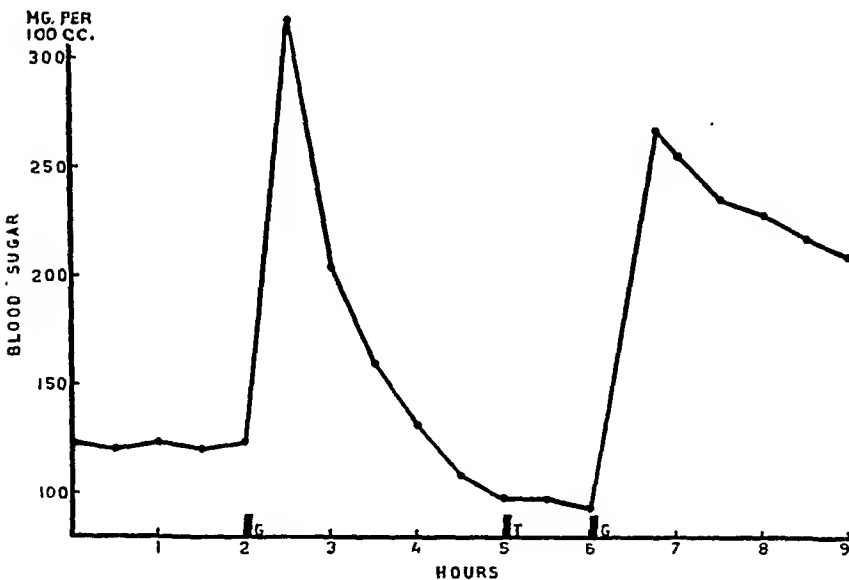


Fig. 2.—Results of tests for dextrose tolerance in a depancreatized dog receiving throughout the experiment a constant injection of dextrose plus insulin just sufficient to maintain the blood sugar at a constant level. G indicates the administration of the test sugar and T the administration of the toxin.

abnormal prolongation of the subsequent dextrose tolerance curve. This effect is probably due to the toxin per se, since it is not obtained with boiled toxin.

2. The normal dextrose tolerance curve obtained in a completely depancreatized dog receiving a constant injection of insulin plus dextrose just sufficient to maintain the blood sugar at a constant level becomes definitely "diabetic" after the administration of toxin.

It is apparent that toxemia does not produce its effects on the dextrose tolerance curve by acting through the pancreas. Furthermore, Yannet and Darrow¹⁰ found no evidence of any gross disturbance in the oxidation of carbohydrates during the course of diphtheritic intoxication produced by the intravenous injection of diphtheria toxin into rabbits. They did observe definite changes in the liver, and they concluded that the observed disturbances in carbohydrate metabolism were due to a failure in hepatic function. Our results support this conclusion and indicate that the hepatic function which is interfered with is that by which the liver normally strives to maintain a constant blood sugar level, by decreasing its own output of sugar in response to the influx of exogenous sugar.

Our work is also in accord with that of Althausen and Thoenes,¹¹ who concluded that the first effect of phosphorus, when given in toxic amounts, was to act as an irritant to the glycogenolytic mechanism of the liver. That this may apply to other functions of the liver is suggested by the findings of Whipple, Peightal and Clark,¹² who reported hypersecretion of phenoltetrachlorophthalein by the liver after small doses of phosphorus were given, which they attributed to the irritative effect of this toxin on the secreting parenchyma. It seems reasonable that this hyperirritability of the liver cells should limit the extent of the hepatic inhibition which normally follows a given rise in blood sugar. However, the limitation of the capacity of the liver to respond in this manner may become evident after the administration of the relatively large test dose of dextrose while the organism, possibly with the aid of other mechanisms of the body, is still able to make a sufficient

10. Yannet, H., and Darrow, D. C.: Physiological Disturbances During Experimental Diphtheritic Intoxication: II. Hepatic Glycogenesis and Glycogen Concentration of Cardiac and Skeletal Muscle, *J. Clin. Investigation* **12**:779 (Sept.) 1933. Yannet, H.; Darrow, D. C., and Goldfarb, W.: Physiological Disturbances During Experimental Diphtheric Intoxication: III. Respiratory Quotients and Metabolic Rate, *ibid.* **12**:787 (Sept.) 1933.

11. Althausen, T. L., and Thoenes, E.: Influences on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes: II. Phosphorus Poisoning, *Arch. Int. Med.* **50**:58 (July) 1932.

12. Whipple, G. H.; Peightal, T. C., and Clark, A. H.: Tests for Hepatic Function and Disease Under Experimental Conditions: Phenoltetrachlorophthalein, *Bull. Johns Hopkins Hosp.* **24**:343, 1913.

adjustment for smaller variations in blood sugar. Hence, a normal blood sugar level may often be maintained in a toxic animal which, nevertheless, yields a "diabetic" tolerance curve.

In their more recent reports, Sweeney and his associates²⁵ concluded that toxemia acts not by merely suppressing the endogenous insulin supply but rather by interfering with the function of insulin, whether it is endogenous or exogenous in origin. This is in entire agreement with our own conclusions in the sense that toxemia interferes with the normal "sensitization" by insulin of the compensatory response of the liver to an increase in blood sugar. To revert to our previous analogy, toxemia represents an interference with the sensitivity of the thermostat. This view of so-called "insulin resistance" removes the therapeutic incongruity of treating already impaired carbohydrate metabolism by the administration of still more carbohydrate. From our standpoint, the treatment with carbohydrate in toxemic states increases the stimulus to the insensitive mechanism. It may be compared to the stimulation of the secretion of urine in the damaged kidney by the administration of urea.

In the light of a previous article which furnishes strong proof for the "overproduction theory" of diabetes mellitus,¹³ this disease may be considered as a condition in which the threshold for the stimulation of the homeostatic mechanism of the liver is abnormally high. The liver, because of an endocrine imbalance,⁵ continues to pour out blood sugar in the presence of even marked hyperglycemia. Since it is the threshold, and not the sensitivity, of the homeostatic mechanism which is affected, the administration of insulin lowers the threshold so that regulation at the normal blood sugar level becomes possible. The success of the more recent diets high in carbohydrates, as advocated by Porges and Adlersberg,¹⁴ Sansum¹⁵ and others, is not surprising when considered in terms of the magnitude of the stimulus to the regulatory mechanism of the liver. However, when infection intervenes, the sensitivity as well as the threshold is affected, and the diabetic organism becomes "insulin resistant." As might be predicted from these results, it has been our experience¹⁶ that the addition of a high intake of carbohydrate may be of great assistance in the treatment of patients with diabetes who are resistant to insulin when the use of large amounts of insulin alone has failed to control the metabolic disturbance.

13. Soskin, S.: The Utilization of Carbohydrate by Totally Depancreatized Dogs Receiving No Insulin, *J. Nutrition* 3:99, 1930.

14. Porges, O., and Adlersberg, D.: *Die Behandlung der Zuckerkrankheit mit fettarmer Kost*, Berlin, Urban and Schwarzenberg, 1929.

15. Sansum, W. D.; Gray, P. A., and Bowden, R.: *The Treatment of Diabetes Mellitus with Higher Carbohydrate Diets*, New York, Harper & Brothers, 1929.

16. Strouse, S., and Soskin, S.: Unpublished data.

CONCLUSIONS

1. The abnormal dextrose tolerance curves occurring in cases of toxemia are due to the effects of the toxin on the liver and not on the pancreas.

2. The toxin interferes with the homeostatic mechanism of the liver which we have described, i. e., the mechanism by which the liver decreases its supply of blood sugar in response to an influx of exogenous sugar.

3. The interpretation of abnormal dextrose tolerance curves in terms of the function of the liver, whether such tests occur in toxemia, diabetes or other conditions, relates all such curves to a common underlying mechanism instead of to various factors as formerly. This not only renders the curves themselves more intelligible but gives a more rational view of "insulin resistance," the use of carbohydrate therapy and other related phenomena.

The Department of Chemistry assisted in the chemical analyses, and Miss Bernice Huddleston gave technical assistance in this study.

DIFFERENTIAL DIAGNOSIS OF RUBELLA

USE OF THE SCHILLING DIFFERENTIAL LEUKOCYTE COUNT

CYRIL M. MacBRYDE, M.D.

AND

CECIL M. CHARLES, M.D.

ST. LOUIS

The differential diagnosis of rubella is of importance for two reasons: first, to distinguish it from toxic rashes and thus prevent the spread of the disease and, second, to distinguish it from scarlet fever and measles and thus permit the care necessary in these more serious conditions. Rubella is usually considered a benign disease. Deaths, however, occur. Carrieu, Lamy and Bouchet¹ reported two fatal cases in young children. Belson² stated that from 1914 through 1929 there were 26 deaths in 35,879 cases reported in Massachusetts.

Complications are rare, but may be serious. Geiger³ described an epidemic in which arthritis was frequent; otitis media, acute nephritis and endocarditis also were observed. Severe symptomatic purpura haemorrhagica with recovery has been described by Pitten⁴ and Gunn.⁵ Suppuration of the cervical lymph nodes, bronchitis and epistaxis occurred in the epidemic reported by Carrieu, Lamy and Bouchet. Involvement of joints, disturbance of the central nervous system and bronchopneumonia occurred in three severe cases reported by Potter.⁶ Lindberg⁷ observed polyarthritis and acute stomatitis as complications. It seems important, considering these possible serious though rare complications, to make every effort to prevent the spread of the disease by making an accurate diagnosis.

From the Department of Medicine, Washington University School of Medicine, and the City Isolation Hospital.

1. Carrieu, Lamy and Bouchet: *La rubéole*, *Presse méd.* **36**:274 (March 3) 1928.

2. Belson, M. O.: *Clinical Features of an Epidemic of Rubella*, *New England J. Med.* **203**:1076 (Nov. 27) 1930.

3. Geiger, J. C.: *Epidemic of German Measles in City Adjacent to an Army Cantonment*, *J. A. M. A.* **70**:1818 (June 15) 1918.

4. Pitten, T.: *Ueber einen Fall von symptomatischem Morbus Werlhof nach Röteln*, *Arch. f. Kinderh.* **86**:114 (Jan. 25) 1929.

5. Gunn, W.: *Case of Rubella Complicated by Purpura Haemorrhagica*, *Brit. J. Child. Dis.* **30**:111 (April-June) 1933.

6. Potter, O.: *Severe Forms of Rubella*, *Brit. M. J.* **2**:1084 (Dec. 27) 1930.

7. Lindberg, G.: *Beiträge zur Nosologie der Rubeola*, *Acta paediat.* **4**:1, 1925.

The exanthem of rubella may at times be characteristic, but in many cases it is difficult to distinguish it from that seen in measles, scarlatina or toxic rashes. The chief criteria usually employed in differential diagnosis are:

Rubella.—The incubation period is seventeen or eighteen days. Enlargement of lymph nodes in the cervical, mastoid and occipital regions begins several days before the appearance of the rash. The rash is discrete and papular, with smaller papules than in measles, and is pink rather than red. It fades in from one to three days. There are few constitutional symptoms and little fever.

Measles.—The incubation period is fourteen days. The onset is preceded by catarrhal symptoms. Koplik's spots are present. The rash consists of dark red macules which become maculopapular and occur in crescentic blotches. Constitutional symptoms may be marked. The temperature is from 102 to 104 F. The rash remains longer than in rubella. Sometimes there is desquamation, and usually there is pigmentation.

Scarlatina.—There is a seven day incubation period. The onset is abrupt, with sore throat, high fever and vomiting. There are a circum-oral pallor and a fine red macular rash which becomes confluent and is more marked in the folds. There are severe constitutional symptoms. Desquamation occurs.

Toxic Rashes.—These have an irregular distribution and are polymorphic. Usually there is no glandular enlargement or fever.

We have found that the differential leukocyte count, with the use of Schilling's classification, is an additional and important diagnostic aid. We believe that failure to recognize a characteristic differential blood picture in rubella has resulted from: (1) misleading observations of early authors, (2) the lack of a practical and satisfactory classification of the leukocytes for clinical purposes, now available in the Schilling count and (3) the lack of careful serial counts throughout the disease in a large number of cases.

Many textbooks⁸ state that the changes in the blood are similar to those in measles and consist of a tendency to leukopenia, an increase in monocytes and lymphocytes and the occurrence of plasma and Türk cells. Dowd⁹ states that there is no characteristic change in the blood

8. Pepper, O. H. P., and Farley, D. L.: *Practical Hematological Diagnosis*, Philadelphia, W. B. Saunders Company, 1933, p. 440. Todd, J. C., and Sanford, A. H.: *Clinical Diagnosis by Laboratory Methods*, Philadelphia, W. B. Saunders Company, 1932, p. 259. Piney, A.: *Diseases of the Blood*, Philadelphia, P. Blakiston's Son & Co., 1928, p. 153. Osgood, E. E., and Haskins, H. D.: *Textbook of Laboratory Diagnosis*, Philadelphia, P. Blakiston's Son & Co., 1931, p. 184.

9. Dowd, H. L.: Rubella, in Cecil, R. L.: *Textbook of Medicine*, Philadelphia, W. B. Saunders Company, 1933, p. 301.

in rubella. Schilling¹⁰ asserted that the "gay" blood picture occurs, but gave no sample counts.

Naegeli¹¹ stated that plasma cells are present in very large numbers, sometimes reaching 30 per cent. This observation focused the attention of succeeding hematologists on the bizarre plasma and Türk cells rather than on changes perhaps more characteristic. Hickling,¹² in fourteen differential counts taken at various stages of the illness in eleven cases, observed no characteristic change except increased plasma cells (averaging 4.5 per cent). His total leukocyte counts varied from 6,900 to 13,700. Eosinophils averaged 2.4 per cent. Lindberg⁷ observed leukopenia early in the disease (from 4,000 to 8,000 leukocytes). Plasma cells occurred in 76 per cent of his cases but averaged only 1.5 per cent. Eosinophils averaged from 1 to 1.5 per cent. He gives this as a typical count: white cells, 5,300 per cubic millimeter; polymorphonuclears, 65 per cent; lymphocytes, 30 per cent; basophils, 2 per cent; eosinophils, 1 per cent, and plasma cells, 2 per cent.

Carroll¹³ observed leukopenia on the first day, an increase in the eosinophils on the third to the fifth day and a rise in the lymphocytes from the fourth to the fifth day onward. He stated that the polymorphonuclear neutrophils are not much affected except for a moderate reduction in number from the fourth or fifth day to the sixth or seventh day. He observed that plasma cells were increased, reaching a maximum of from 3 to 11 per cent on the third day. Türk cells were increased, but were less numerous and less constantly present.

Considerable confusion will be seen to result if an attempt is made to correlate and interpret the observations of the various authors cited.

During the spring months of 1932 and 1933 serial counts by the Schilling method were done in thirty cases of rubella throughout the course of the disease. A clear picture soon began to present itself as characteristic. This was very different in the early stages from that obtained in scarlatina, measles or toxic rashes.

The supposedly characteristic plasma and Türk cells were entirely absent from many slides. Lindberg⁷ observed that they were absent in one fourth of his cases. These cells are difficult to identify, and hematologists differ greatly in describing them. The plasma cell has abundant basophil cytoplasm, usually vacuolated, and an eccentric

10. Schilling, V.: *The Blood Picture and Its Clinical Significance*, translated by R. B. H. Gradwohl, St. Louis, C. V. Mosby Company, 1929, pp. 268 and 297.

11. Naegeli, O.: *Blutkrankheiten und Blutdiagnostik*, Berlin, Julius Springer, 1923.

12. Hickling, R. A.: *The Significance of Hemic Plasma Cells in Various Infective Conditions*, *J. Hyg.* **24**:120 (Oct.) 1925.

13. Carroll, John V.: *The Blood Count in Rubella*, *Lancet* **1**:182 (Jan. 27) 1934.

nucleus bordered by a clear space in the cytoplasm (*Zellhof*). The Türk irritation cell morphologically comes between the plasma cell and the lymphocyte. It is often difficult to distinguish a plasma cell, a Türk cell and a lymphocyte with deep basophil cytoplasm. The Türk cell has no vacuoles or *Zellhöfe* and is the same size or slightly larger than the average lymphocyte. The nucleus is usually eccentric. The Türk cell stains more evenly, while the plasma cell is characteristically foamy. Piney¹⁴ stated that the Türk cell is a modified lymphocyte, but that it is uncertain whether it is a stage in the development of the plasma cell.

Since there is considerable disagreement as to the appearance of these cells, and since even experienced hematologists have difficulty at times in distinguishing them from lymphocytes, to which they are closely related, we have included both plasma and Türk cells with our lymphocytes in the tables. A system of hematologic diagnosis must be simple to be useful. The differential diagnosis of the exanthems is the general practitioner's problem. He cannot be expected to identify unusual forms of cells, but the simple principles of the Schilling classification are easily learned and used.

We observed plasma cells occurring inconstantly, reaching 6 per cent in one case on the third day, but averaging about 2 per cent in the early days. Türk cells averaged about 1 per cent. We agree with Hickling¹² and Carroll¹³ that these cells appear also in measles, but in smaller numbers and less constantly. For those prepared to identify them they are an additional aid in diagnosis.

We found no significant differences between the counts in children and adults. Our youngest patients were two, aged 7. No complications were observed in our series of thirty cases.

Table 1 gives the sérial counts on successive days of the disease, the date of onset being considered the day of appearance of the rash. At the onset the neutrophils constitute only about 60 per cent of the white cells, but there is a marked rise in the stab cells. The appearance of juvenile forms (metamyelocytes) is rare. The lymphocytes and monocytes are relatively numerous, while eosinophils tend to be retained in normal numbers, not disappearing as in most acute infections. The total white cell count averages less than 5,000 per cubic millimeter, but some counts fall within the normal range. As the mild elevation in temperature subsides and the rash disappears the total neutrophil count falls, reaching a low point of about 48 per cent on the fourth day. The percentage of stab cells rapidly falls, reaching normal between the eighth and twelfth days. Meanwhile the lymphocytes and monocytes rise, reaching a maximum about the fourth day. The eosinophils rise, reaching a maximum averaging 2 per cent but sometimes reaching 10 per cent, between the third and sixth days. The total leukocytes rise

14. Piney, A.: Plasma Cell Leukemia, *Folia haemat.* **30**:173 (Aug.) 1924.

TABLE 1.—Serial Differential Blood Counts in Rubella

Day	Number of Patients	Baso- phils		Eosinophils		Myelo- cytes	Juvenile Forms	Stab Cells		Segmented Forms		Lymphocytes		Monoocytes		White Cells	
		Average	Range	Average	Range			Average	Range	Average	Range	Average	Range	Average	Range	Average	Range
1	11	0	0-0	0.9	0-4	0	0	15.4	9-19	44.7	30-54	34.6	25-48	4.8	1-12	4,982	3,450-7,800
2	23	0	0-4	1.1	0-4	0	0	14.4	8-24	41.7	26-54	33.0	23-50	4.9	2-8	5,441	3,300-9,000
3	25	0	0-5	1.9	0-5	0	0	11.8	5-18	40.6	25-62	39.9	21-58	5.7	3-9	5,844	4,150-8,900
4	22	0	0-5	1.9	0-5	0	0	8.4	5-16	39.6	19-60	43.7	23-62	6.0	2-10	7,690	6,400-9,000
5	18	0	0-10	2.1	0-10	0	0	6.9	2-13	43.8	32-63	42.8	28-59	5.3	2-9	7,950
6	21	0	0-4	2.0	0-4	0	0	5.5	3-11	46.1	30-61	41.2	26-58	4.7	1-10	7,833	6,250-9,250
7	16	0	0-4	1.9	0-4	0	0	5.3	3-9	48.6	32-65	39.6	23-56	4.6	2-8	8,350	8,100-8,600
8	9	0	0-3	1.3	0-3	0	0	4.8	2-8	51.3	36-64	38.1	24-52	4.3	2-6	9,150

gradually from the first day onward, reaching normal about the seventh or eighth day. By the eighth day a definite approach toward normal is apparent in all respects, and within the next few days normal figures are reached.

TABLE 2.—*Typical Counts in Rubella* *

Day	Baso- phils	Eosino- phils	Myelo- cytes	Juvenile Forms	Stab Cells	Segmented Forms	Lympho- cytes	Mono- cytes
1	0	0	0	0	18	46	32	4
2	0	0	0	0	11	41	41	7
3	0	1	0	0	10	37	49	4
4	0	3	0	0	8	42	32	9
5	0	0	0	0	8	46	41	5
6	0	1	0	0	4	60	34	1
7	0	1	0	0	6	54	31	8

* The patient was a white man, aged 30. The total leukocyte count on the first day was 3,650. The rash and fever were gone by the third day.

TABLE 3.—*Typical Counts in Measles* *

Day	White Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juvenile Forms	Stab Cells	Segmented Forms	Lympho- cytes	Mono- cytes
1	6,200	0	1	0	4	12	55	25	3
2	6,000	0	2	0	6	16	55	21	0
3	6,300	0	2	0	3	14	60	19	2
4	6,100	0	0	0	0	10	63	23	4
6	6,800	0	2	0	0	9	57	27	5
8	7,200	0	1	0	0	10	55	30	4
10	8,400	0	0	0	0	8	53	36	3
12	8,100	0	2	0	0	8	46	41	3
14	8,250	0	1	0	0	4	58	33	4

* The patient was a white boy, aged 12. The temperature was 102 F. on the first day, 103 F. on the second day, and 101 F. on the third day. On the fourth day the fever was gone. On the sixth day the rash was gone.

TABLE 4.—*Typical Counts in Scarlatina* *

Day	White Cells	Baso- phils	Eosino- phils	Myelo- cytes	Juvenile Forms	Stab Cells	Segmented Forms	Lympho- cytes	Mono- cytes
1	18,200	0	2	0	8	20	56	14	0
2	14,400	0	2	0	6	18	56	18	0
3	12,100	0	4	0	3	15	55	20	3
4	11,000	0	5	0	0	10	58	21	6
5	10,000	0	3	0	0	9	62	20	6
6	11,200	0	1	0	0	9	62	19	9
7	8,000	0	0	0	0	8	62	25	5
10	8,300	0	1	0	0	6	53	36	4
12	7,600	0	1	0	0	4	61	30	4
14	8,800	0	1	0	0	3	62	30	4

* The patient was a white boy, aged 7.

Table 2 gives the counts in a typical case of rubella occurring in a white man, 30 years old.

When the counts in rubella are compared with those obtained in typical cases of scarlatina, measles and toxic rashes, definite differences are at once apparent (tables 3, 4 and 5).

In measles (the counts by Hickling,¹² Bunting and Thewlis¹⁵ and Schilling¹⁰ are similar to ours) there is less tendency to leukopenia; there is a more marked "defense reaction" with a higher number of neutrophils, among which stab cells are more numerous and juvenile forms appear. Lymphocytes are correspondingly less numerous. Monocytes and eosinophils tend to follow curves similar to those in rubella. The higher neutrophil count, with the appearance of juvenile forms,

TABLE 5.—*Typical Counts in Toxic Rash (Drug?) **

Day	White Cells	Basophils	Eosinophils	Myelocytes	Juvenile Forms	Stab Cells	Segmented Forms	Lymphocytes	Monocytes
1	10,000	0	3	0	0	6	68	20	3
2	9,400	0	6	0	0	5	69	18	2
3	8,300	0	2	0	0	4	60	31	3
4	8,350	0	3	0	0	2	56	37	2
5	8,200	0	2	0	0	3	57	35	2

* The patient was a white boy, aged 8. The rash resembled that of both scarlet fever and measles. It lasted for four days. There was no fever.

TABLE 6.—*Rubella Followed by Scarlatina **

Day	White Cells	Eosinophils	Stab Cells	Segmented Forms	Lymphocytes	Monocytes	Comment
3	6,700	0	18	33	41	8	Note fall in stab cells and rise in lymphocytes during recovery from rubella
4	1	11	45	40	3	
5	1	11	50	34	4	
6	1	11	52	32	4	Lymphocytes fall suddenly; segmented forms increase, and fall in stab cells is arrested
7 (first day of scarlatina; sore throat)	1	9	57	29	4		
8 (second day of scarlatina; rash appeared)							
9	19,450						
10	12,550						
11	1	9	69	16	5	
12	1	8	63	24	4	

* The patient was a white girl, aged 19. Both the rubella and the scarlatina were typical and uncomplicated.

and the relatively low percentage of lymphocytes should be helpful in distinguishing doubtful cases from rubella.

In scarlet fever there is a very high leukocyte count with a very high count for total neutrophils, stab cells typically reaching 20 per cent or more and juvenile forms 8 per cent or more. Lymphocytes are low, being 14 per cent or less. Eosinophils tend to be retained and to rise during recovery. The blood differential count in scarlet fever should never be confused with that in rubella.

15. Bunting, C. H., and Thewlis, E.: Leukocytic Reactions in Smallpox, Chickenpox, Measles and Mumps, Arch. Path. 1:189 (Feb.) 1926.

In drug or toxic rashes the total leukocyte count may be slightly increased, with a slight rise in neutrophils and stab cells. Eosinophils are usually increased.

Of the greatest importance in the study of differential leukocyte counts in acute infections is the recognition that the hemogram may change considerably from day to day, and that counts must be inter-

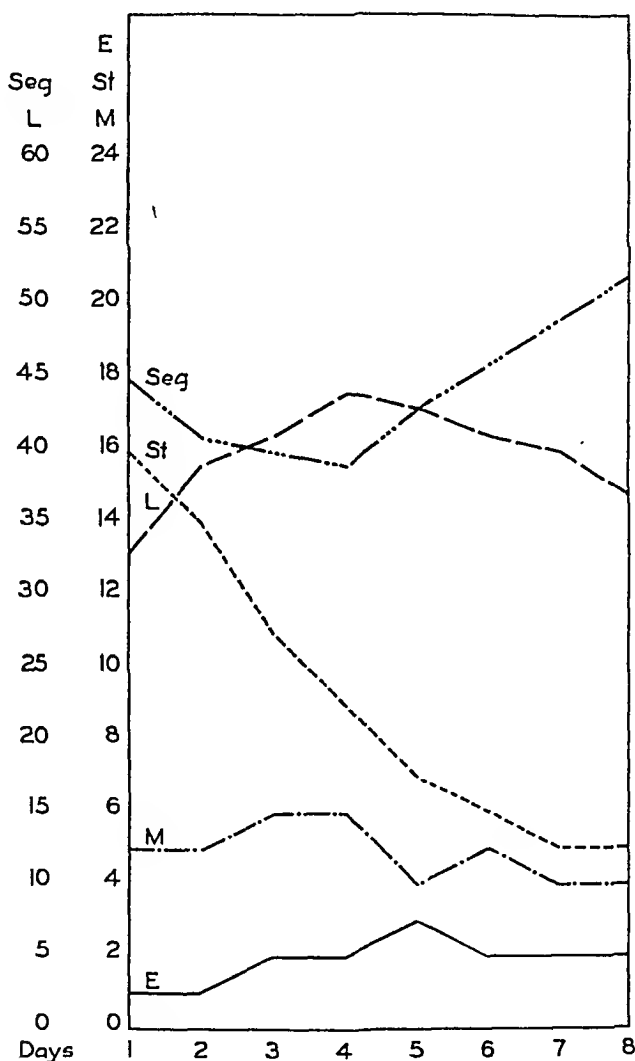


Chart 1.—Curve showing changes in the leukocyte count in rubella. In this chart and in chart 2 the letters have the following meanings: *E* indicates eosinophils; *St*, stab forms; *Seg*, segmental forms; *L*, lymphocytes; *M*, mononuclears, and *J*, juvenile forms.

preted according to the stage and duration of the illness. Curves charting the changes in rubella and measles serve to emphasize that the rapidity of rise and fall of the various component classes of leukocytes,

as well as the actual percentage of height, is helpful in making the diagnosis.

In one of our patients scarlatina developed immediately following the attack of rubella. The rapid rise in the neutrophils and fall in the lymphocytes, while the stab cells were arrested in their rapid fall, are well seen in table 6.

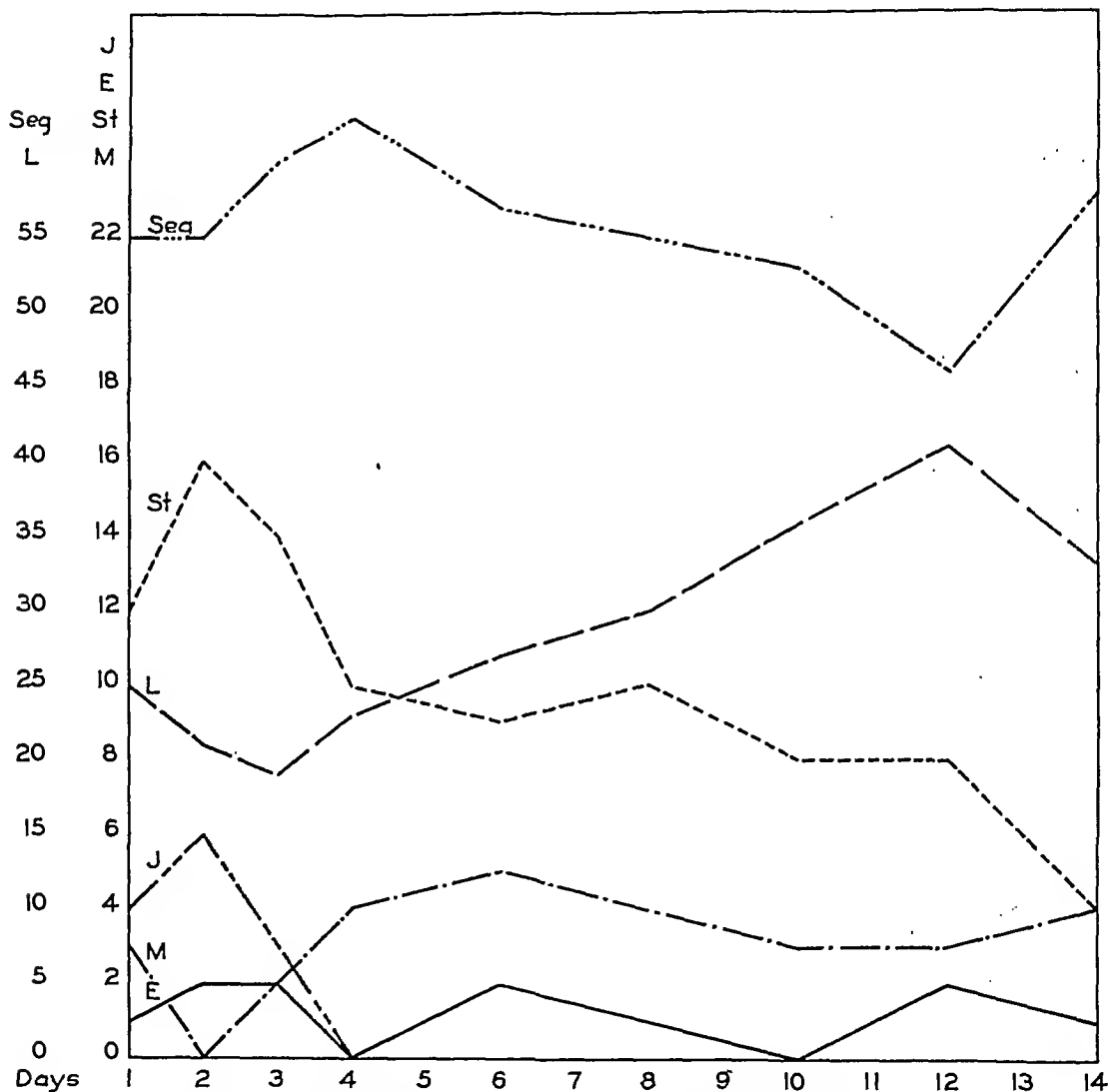


Chart 2.—Curves showing changes in the leukocyte count in measles.

CONCLUSIONS

1. In a study of thirty cases of rubella the use of the Schilling differential leukocyte count was found to be an important aid in making the diagnosis.

2. Serial differential counts in measles, scarlatina and toxic rashes—conditions which may be confused with rubella—differ significantly from counts obtained in rubella.

RENAL AMYLOIDOSIS

CLINICAL COURSE AND PATHOLOGIC LESIONS IN SIXTEEN CASES

HUGO O. ALTNOW, M.D.

MINNEAPOLIS

AND

CHARLOTTE C. VAN WINKLE, M.D.

HENRY W. MALY, M.D.

AND

LOWELL E. WILLIAMS, M.D.

OAK TERRACE, MINN.

While renal amyloidosis is a common complication of tuberculosis, apparently it has not received much attention from English-speaking physicians, so far as published reports are concerned. Reports of only 14 cases of amyloid in the kidneys were found in a review of the literature from Jan. 1, 1917, to Dec. 31, 1932. We found the following cases reported, including those of both tuberculous and nontuberculous origin:

Noble and Major¹ reported 3 cases, 2 of which occurred in conjunction with chronic osteomyelitis (presumably nontuberculous) and 1 of which was of undetermined etiology. Cabot² reported a case in which there was unexplained fever of four months' duration. Necropsy revealed abdominal lymphadenopathy with ascites. The pathologic report on a lymph gland was "chronic inflammation." Christian³ reported a case in which no cause for the general amyloidosis could be found. Shapiro⁴ reported 1 case of a patient with tuberculous arthritis of both shoulders. Whitbeck⁵ reported 7 cases of general amyloidosis occurring in tuberculosis of the bones. In one report it is stated that the urine contained albumin (four plus). In the others the results of urinalysis are not mentioned. He was more interested in other phases of the disease than

From the Nicollet Clinic of Minneapolis and the Glen Lake Sanatorium, Oak Terrace.

1. Noble, J. F., and Major, S. G.: Renal Insufficiency in Amyloid Disease, *Arch. Path.* **8**:762 (Nov.) 1929.

2. Cabot, R. C.: Albuminuria and Unexplained Sepsis, *New England J. Med.* **201**:833 (Oct. 24) 1929.

3. Christian, H. A.: The Nephrosis Syndrome Associated with Idiopathic Amyloidosis, *M. Clin. North America* **15**:805 (Jan.) 1932.

4. Shapiro, P. F.: Lipoid Nephrosis: Pathology, Genesis and Relation to Amyloidosis, *Arch. Int. Med.* **46**:137 (July) 1930.

5. Whitbeck, B. H.: Liver Meal in Treatment of Amyloidosis in Surgical Tuberculosis, *J. Bone & Joint Surg.* **14**:85 (Jan.) 1932.

in the renal phase. Walker⁶ cited a case with empyema of the lung in which the diagnosis was based on the presence of a large liver and spleen and albuminuria. The patient recovered five years after the onset. Linder, Maxwell and Green⁷ reported a case following disease of the mastoid, with long continued suppuration. Bell⁸ reported a case of renal amyloidosis of undetermined origin. Addis and Oliver⁹ reported 5 cases under the diagnosis of the "pyogenic form of degenerative Bright's disease," 1 of which occurred in association with advanced pulmonary tuberculosis, 2 with tuberculosis of the bones and 2 with chronic osteomyelitis. Williams, who was mentioned by Holten, evidently had considerable personal experience with renal amyloidosis, but we were unable to locate his published material. In the German literature, Kieffer¹⁰ reported 45 cases of clinical nephrosis from a tuberculosis clinic, in 42 of which it was proved at necropsy that there were amyloid deposits in the kidneys. Simon¹¹ reported 43 cases of nephrosis, presumably with amyloid change in the kidney, occurring in association with tuberculosis of the bones and joints and with non-pulmonary tuberculosis. In 17 of 25 fatal cases the patients were examined at necropsy, and we assume that they had proved cases. He mentions only 1 case occurring in association with other forms of tuberculosis in his experience, namely, in 1 with a case of intestinal tuberculosis with a perirectal abscess. Fahr¹² reported 10 cases, all of which showed the glomerular lesions of nephritis combined with amyloidosis of the kidneys. Two of these occurred in conjunction with tuberculosis, 4 with syphilis and 4 in patients with other infections and suppurative processes. In the Scandinavian literature, Holten¹³ reported 30 cases, 3 of which were cases of hemorrhagic nephritis with amyloid disease;

6. Walker, G. F.: Case of Recovery from Amyloid Disease, *Lancet* **2**:120 (July 21) 1928.

7. Linder, G. C.; Maxwell, J., and Green, F. H. K.: Clinical, Pathological and Biochemical Study of Amyloid Nephrosis, *Arch. Dis. Childhood* **2**:220 (Aug.) 1927.

8. Bell, A. W.: Amyloid Infiltration, *Journal-Lancet* **42**:306 (June 15) 1922.

9. Addis, T., and Oliver, J.: The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931.

10. Kieffer, O.: Kidney Disease in Pulmonary Tuberculosis, *Ztschr. f. Tuberk.* **33**:9, 65 and 137, 1920.

11. Simon, S.: Zur Klinik der Nephrose bei Knochen- und Gelenktuberkulose, *Deutsches Arch. f. klin. Med.* **163**:87, 1929.

12. Fahr, T.: Zur Frage der Nephrose, *Berl. klin. Wchnschr.* **55**:993, 1918; Ueber atypische Befunde aus den Kapiteln des Morbus Brightii nebst anhangsweisen Bemerkungen zur Hypertonie-frage, *Virchows Arch. f. path. Anat.* **248**:323, 1924; Zur Frage der Amyloidnephrose und Amyloidschrumpfnieren, *Klin. Wchnschr.* **10**:1205 (June 27) 1931.

13. Holten, C.: Nephritis Caused by Tuberculosis, *Acta med. Scandinav.* **61**:107, 1924.

4, of amyloid disease with renal tuberculosis (all these cases were proved by necropsy), and 23, of renal amyloidosis, with 18 fatal cases, in 17 of which necropsy was performed. In the French literature there are several reports of 1 and 2 cases, but no series of cases is reported. Rosenblatt¹⁴ reported 125 cases of amyloidosis, 110 of which occurred in association with tuberculous, and 15 with nontuberculous, conditions. Of this number, 87 showed amyloid deposits in the kidney. His observations extend over 1927 to 1932, which is the same period covered by our study. Many of his findings are similar to ours, and each study corroborates many of the observations of the other. We have, however, approached the matter of diagnosis from a somewhat different angle and have been more interested in portraying the life history of the disease in the individual patient.

PATHOLOGIC AND CLINICAL DIAGNOSIS

This paper is confined to a study of 16 cases of renal amyloidosis in which a clinical diagnosis was made during life and confirmed by post-mortem observation of amyloid deposits in the kidney. The presence of amyloid was considered established when demonstrated by a methyl violet stain in the microscopic sections. The hematoxylin and eosin stain and the iodine reaction in fresh and formaldehydized tissues were also utilized for its demonstration. In 4 cases (6, 11, 14 and 15) intravital staining with congo red was still present from congo red injected before death. In the last 3 cases the dye was injected four, eleven and sixteen months before death, respectively. In all the cases amyloid was demonstrated in the liver and spleen by the methyl violet stain, except in the liver in case 8.

As a result of five years' experience, we believe that if in the course of advanced pulmonary tuberculosis complicated by a suppurative process, tuberculous enteritis, tuberculosis of the serous membranes or any other major complication, or, in the course of tuberculosis of the osseous system, both albumin and casts appear in the urine in considerable amounts, a diagnosis of renal amyloidosis may be entertained with the expectation that further study will confirm it. If, associated with these changes, the liver and spleen are enlarged, the diagnosis may be considered reasonably well established.

If the liver and spleen are not enlarged, the presence of edema, normal or low blood pressure, hyposthenuria, a normal output of dye, normal nonprotein nitrogen and normal eyegrounds support the diagnosis.

14. Rosenblatt, M. B.: Amyloidosis and Amyloid Nephrosis, *Am. J. M. Sc.* 86:558 (Oct.) 1933.

If either pus cells or red blood cells are found in considerable numbers in addition to the albumin and casts, if the output of dye is diminished and nitrogen retained and if the blood pressure is elevated and the liver and spleen are enlarged, the diagnosis may be considered established, with only a slight possibility of error. On the other hand, if the liver and spleen are not enlarged, the diagnosis must be made with considerable hesitation. In this group the consideration of the clinical history, together with the clinician's experience in evaluating the many factors that may come into play, may turn the balance in favor of the diagnosis.

Proceeding in this manner, the usual acute glomerular nephritis and acute and chronic hemorrhagic nephritis may be readily differentiated, if encountered. Lipoid nephrosis and the chronic glomerular and chronic vascular types of nephritis offer greater difficulty. With these types the congo red test may be very helpful in differentiation. However, clinical experience again weighs the evidence in one direction or the other.

Looking back on our experience, especially in the cases in which a diagnosis was not made during life, we believe that in cases in which we overlooked the diagnosis we failed to suspect renal amyloidosis because we did not attach enough importance to the appearance of albuminuria and cylindruria in patients with complicated advanced tuberculosis.

SELECTION OF CASES

The following procedure was followed in the selection of cases of renal amyloidosis for study:

In the Glen Lake Sanatorium a morning specimen of urine is submitted as a routine to chemical and microscopic examination on the patient's admission and once in three months during his residence. All these reports were checked in a routine manner for albuminuria and cylindruria. When either of these was reported present, three specimens of urine were examined at weekly intervals by us. If both albuminuria and cylindruria were present in the three specimens examined, the case was considered one of probable renal amyloidosis and selected for study of the blood pressure, renal function, special physical examination and examination of the eyegrounds. The time when both albumin and casts appeared and remained more or less constant was designated as the "definite" onset of amyloidosis. If either albumin or casts appeared and remained more or less constant, we designated the time of appearance as the "presumptive" onset. Using these criteria and the routine laboratory records, we have in some cases antedated the time of the presumptive and definite onset from the time that the clinical diagnosis was actually made (table 2 and charts for cases 1 to 16). A chart showing the average specific gravity of the urine in all the cases, charts showing the results of tests in each case and photomicrographs of a section of the kidney in each case are to be found at the end of this article.

NATURE OF THE TUBERCULOSIS IN WHICH RENAL
AMYLOIDOSIS OCCURS

Eleven of 16 cases (table 1) were those of far advanced pulmonary tuberculosis with cavity formation; 2, of moderately advanced pulmonary tuberculosis, 1 with cavity formation, and 3, of Pott's disease with psoas abscesses. Case 13 deserves special comment. In the beginning it was classified as a case of moderately advanced pulmonary tuberculosis. The onset previous to admission was marked by hemoptysis. Shortly afterward tubercle bacilli were found in the sputum, and after admission laryngitis developed. Carcinoma of the lung, however, completely overshadowed the tuberculosis the last two years of the illness. We believe that the carcinoma with necrosis and metastasis to bone was responsible for the deposit of amyloid.

With the exception just noted, all the patients had one or more tuberculous complications. Table 1 shows the complications noted clinically and at postmortem examination. The symbols indicate whether the diagnosis was made clinically or post mortem or clinically and confirmed post mortem. Patient 9 had the largest number, namely, eight. All told, fifty-five complications of tuberculosis occurred in the 16 patients. The most prominent complication was enteritis. In 10 cases the diagnosis was made during life, and in 2 others at autopsy only. Of the 10 patients for whom a diagnosis was made ante mortem, 3 (8, 9 and 11) showed tuberculous enteritis at autopsy; 3 (4, 10 and 15) showed amyloid infiltration in the intestine, which conceivably accounts for the clinical diagnosis, and the remaining 4 (1, 5, 12 and 14) had definite symptoms which referred to the gastro-intestinal tract and had roentgen findings which suggested tuberculous enteritis. We believe that amyloid infiltration of the intestine may produce diarrhea and other gastro-intestinal symptoms and simulate tuberculous enteritis. At least the occurrence of diarrhea and gastro-intestinal symptoms in far advanced tuberculosis should suggest the possibility of coexisting renal amyloidosis. Kieffer¹⁰ stated that "almost all" his patients had intestinal tuberculosis. Seven other tuberculous complications occurred in the digestive tract, namely, five of the rectum and two in the appendix.

The most frequent postmortem complication was tuberculous adenitis. This was present in twelve cases, but in only 2 cases were the accessible lymph glands enlarged to the extent that a clinical diagnosis of tuberculous adenitis was made. Tuberculosis of the serous membranes forms an important group, pleurisy with effusion having occurred in 6 patients, empyema in 3, pericarditis in 4 and peritonitis in 2, involving 10 cases in all. The only other noteworthy complication is laryngitis, which occurred in 6 cases. There was confirmation at autopsy in only 1 case, but the larynx is not examined as a routine at postmortem examination at this sanatorium.

TABLE 1.—Primary Lesions and Suppurating Focus with Complication Noted Clinically and at Autopsy, Exclusive of Amyloidosis*

CASE	Primary Diagnosis	Tuberculous Lesions					Scrous Membrane			Other Lesions
		Gastro-Intestinal Tract			Adenitis	Pleural Effusion	Pericarditis	Tuberculous Peritonitis		
		Suppurating Focus	Enteritis	Appendix						
					Rec-tum	Larynx				
1	Far advanced pulmonary tuberculosis with cavitation (ca)	c	..	c	c	a	
2	Pott's disease (ca)	ca	c	..	
3	Pott's disease (ca)	a	a	..	
4	Far advanced pulmonary tuberculosis with cavitation (ca)	c	a	a	a	..	
5	Far advanced pulmonary tuberculosis with cavitation (ca)	c	..	ca	..	a	Nontuberculous abscess (a)
6	Far advanced pulmonary tuberculosis with cavitation (ca)	a	a	a	ca	..	Tuberculous kidney (ca)
7	Far advanced pulmonary tuberculosis (ca)	a	a	a	Miliary tuberculosis (a)
8	Far advanced pulmonary tuberculosis with cavitation (ca)	ca	a	..	c	a	Syphilis (c)
9	Far advanced pulmonary tuberculosis with cavitation (ca)	ca	..	a	c	a	..	a	Tubercle of heart (a)
10	Far advanced pulmonary tuberculosis with cavitation (ca)	c	a	ca	a	Retropertitoneal abscess (a)
11	Far advanced pulmonary tuberculosis with cavitation (ca)	ca	ca	ca	..	Tuberculous bronchiectasis (c)
12	Far advanced pulmonary tuberculosis with cavitation (ca)	c	c	..	a	a	Otitis media (c)
13	Moderately advanced pulmonary tuberculosis (c)	c	
14	Moderately advanced pulmonary tuberculosis with cavitation (ca)	c	..	c	..	a	c	a	Syphilis (c)
15	Pott's disease (ca)	c	a	Gardnoma of lungs (a)
16	Far advanced pulmonary tuberculosis with cavitation (ca)	a	a	Metastasis to bone (a)

* c indicates clinical diagnosis; a, observation at autopsy, and ca, clinical diagnosis confirmed at autopsy. Amyloid was present in the intestinal wall in cases 4, 7, 8, 9, 10 and 15.

All but 4 of the patients showed another renal lesion. Two showed open tubercles, as diagnosed by the inoculation of guinea-pigs with urine. One patient had a terminal suppurative nontuberculous abscess of the kidney. Eight patients showed renal insufficiency (chronic nephritis), which was slight to marked on renal function tests, and which in all cases was confirmed at postmortem examination. One additional patient (9) showed postmortem evidence of chronic nephritis. The nonprotein nitrogen of the blood in this case was 29 mg. per hundred cubic centimeters three months prior to death.

PROBABLE PRECIPITATING COMPLICATION

After determination of the presumptive and definite onset of renal amyloidosis, as previously described, we were interested in trying to determine whether any unusual event in the clinical history of the patient could be associated with the renal complication. The complications that appear to stand in rather intimate relationship or coincidental with the onset of renal amyloidosis are in bold face type in table 2. The date of onset thus related is also in bold face type. In cases 1, 5, 8, 9 and 12 the evidence of renal amyloidosis occurred either with, or not longer than three months after, the onset of clinical enteritis. In case 2 the development of the psoas abscess preceded the onset by two months. Patient 3 was admitted with a draining tuberculous spine. At that time he also had a slight albuminuria. In September 1927 the abscess closed and had to be aspirated and reopened. A month later the urine showed both albuminuria and cylindruria.

In case 7 albuminuria followed tuberculous empyema after a short interval, and in cases 11 and 13 albuminuria followed pleural effusion, in the latter following the institution of pneumothorax. Patient 4 had a hemorrhage in June 1930, phrenicphraxis on the left side and pneumothorax in July, and in August marked albuminuria and cylindruria. Patient 10 had slight intermittent albuminuria and cylindruria for nine years, but following thoracoplasty in May 1930 severe albuminuria and cylindruria developed. Patient 14 had cylindruria that was slight to moderate from March 1918 to November 1931. In August 1918 he had a slight albuminuria. In November 1921 he had a flareup of his tuberculosis. In December 1921 there was an abrupt onset of marked albuminuria, which persisted until death, eleven years later. Patient 16 in September 1929 showed an extension of his tuberculosis, and simultaneously a moderate number of hyaline casts appeared in the urine; October 1931 marked the onset of albuminuria.

Patient 11, who has already been mentioned, presented a remarkable feature worthy of further comment. In June 1930 purulent pleural effusion developed. The following month a moderate number of hyaline

casts appeared in the urine, which were present for four months. Repeated aspirations brought about marked clinical improvement, and the urine showed no casts for thirteen months. Then he had a high temperature and a marked spread of his tuberculosis, at which time the cylindruria reappeared and albumin was present.

TABLE 2.—*Clinical Events and Onset of Renal Amyloidosis*

Case	Clinical Events		Date of Presumptive Onset of Renal Amyloidosis	Date of Definite Onset of Renal Amyloidosis
	Date	Event		
1	Dec. 1924 July 1925 Jan. 1928 March 1928	Tuberculous laryngitis Enteritis Ischlorectal abscess that drained Enteritis	Aug. 1925	Aug. 1930
2	Feb. 1927	Psoas abscess	April 1927
3	On admission (Dec. 1926) Sept. 1927	Draining tuberculous splne Abscess closed; aspirated and opened	Dec. 1926	Oct. 1927
4	June 1930 July 1930	Hemorrhage Phreniphraxis on the left; pneumothorax	Aug. 1930
5	May 1930	Enteritis	Aug. 1930
6	On read- mission (May 1928)	Draining empyema	May 1928	July 1928
7	On admission (Oct. 1930)	Empyema	Nov. 1930	Jan. 1931
8	Aug. 1930	Enteritis	Sept. 1930
9	Oct. 1928 Dec. 1928	Enteritis Enteritis (second attack)	Oct. 1928	Feb. 1929
10	Nov. 1929 Feb. 1930 March 1930 May 1930	Hemorrhage First stage thoracoplasty Second stage thoracoplasty Third stage thoracoplasty	May 1930
11	March 1930 June 1930 Dec. 1931	Pleural effusion, left side Purulent pleural effusion, right side High fever; extension of tuberculosis	July 1930	Dec. 1931
12	March 1927	Enteritis	March 1927
13	Dec. 1927 Jan. 1928	Pneumothorax Fluid at base of left lung	Feb. 1928
14	Oct. 1921 Nov. 1921	Exercise discontinued Flareup of tuberculosis	April 1918	Dec. 1921
15	On admission (July 1923) Dec. 1924	Psoas abscess Pott's disease	April 1925	March 1928
16	Sept. 1929 Jan. 1930 May 1931	Extension of tuberculosis Bad teeth; pyorrhea Questionable enteritis and slight obstruction	Sept. 1929	Dec. 1931

In only six cases (2, 3, 6, 7, 11 and 15) was the onset preceded by a definite suppurative complication.

The brief interval between the probable precipitating complication and the urinary observations indicating a beginning renal lesion or definite onset of renal amyloidosis is particularly striking in all but 2 cases (6 and 15). In case 6 the date of the onset of albuminuria is not known. Both these patients had a definitely suppurative complication on admission.

ALBUMINURIA

The duration of the albuminuria is shown in table 3. Slight albuminuria includes amounts that were recorded, from the smallest trace to one plus. When the results were recorded as two plus and over, the condition is called severe albuminuria. The total duration of known albuminuria varies from a minimum of three to a maximum of one hundred and seventy-one months, the average being thirty-three, and the median, from fifteen to sixteen months. The severe albuminuria was present from a minimum of one to a maximum of one hundred and thirty-one months, the average being twenty-one, and the median, from nine to twelve months.

TABLE 3.—*Albuminuria*

Case	Total Duration of Albu- minuria, Months	Duration of Severe Albu- minuria, Months	Comment
1	63	2	Albuminuria preceded cylindruria by 30 months
2	12	12	
3	21	3	Albuminuria preceded cylindruria by 9 months
4	12	12	Variable in amount; absent on one occasion
5	16	13	Albuminuria preceded cylindruria by 4 months
6	3 (?)	3 (?)	Tuberculous empyema developed 10 months prior to readmission, which is probable date of onset of renal complication
7	17	16	Albuminuria preceded cylindruria by 2 months
8	4	4	
9	33	6	Albuminuria preceded cylindruria by 5 months
10	4	4	
11	5	1	Cylindruria preceded albuminuria by 17 months
12	44	44	
13	11	9	
14	171	131	Cylindruria preceded albuminuria by 5 months
15	96	62	Albuminuria preceded cylindruria by 34 months
16	15	15	Cylindruria preceded albuminuria by 25 months
Average	32.94	21.06	
Median	15 to 16	9 to 12	

Patient 6 had severe albuminuria on readmission. She had had empyema ten months previously. The onset of the albuminuria probably occurred shortly thereafter, but we are including only the known period.

In 12 cases there were no urinary observations prior to the onset of renal amyloidosis to suggest any previous kidney disease. Patient 5 had a trace of albumin in December 1927, but we mark the onset of his renal amyloidosis as October 1930. Patient 10, from October 1919 to May 1930, had traces of albumin in four specimens of urine and a small number of hyaline casts in two. There was a long interval in which the results of urinalysis were negative—for more than two years before the onset of renal amyloidosis. It is likely that he had slight damage of the kidneys due to mild chronic nephritis. Patient 12 had on one occasion a trace of albumin (in August 1919), with a small number of granular casts. A small number of granular casts were noted again in

1920. The urine then remained normal until March 1927, the time of onset of renal amyloidosis. Mild acute nephritis or amyloidosis with residual damage of the kidneys at that time is a possibility. This is of interest in view of the fact that renal insufficiency developed. Patient 8 had a trace of albumin, together with slight pyuria. Neither albumin nor casts were present until a year later, when renal amyloidosis began. In 6 cases (1, 3, 5, 6, 9 and 15) albuminuria preceded cylindruria by thirty, nine, four, two, five and thirty-four months, respectively. In 3 cases (11, 14 and 16) cylindruria preceded albuminuria by seventeen, five and twenty-five months, respectively. In the other 7 cases the onset was simultaneous. Simon¹¹ stated that albuminuria always precedes

TABLE 4.—*Urinary Sediment*

Case	Duration of Slight Cylindruria (Few Casts to 1+), Months	Duration of Severe (2+ to 4+), Months	Variety of Cast		White Blood Cells	Red Blood Cells
			Hyaline	Granular		
1	30	2	+++	±	1+ to 4+	0
2	12	7	++	+	±	0
3	12	12	++	+	±	+
4	12	12	++	±	1+	0
5	13	11	+++	+	±	0
6	1	1	++++	—	1+ to 4+	0
7	15	15	—	+++	4+	+
8	4	4	++++	—	±	0
9	28	9	+++	±	±	0
10	4	1	+	+	±	Once*
11	22	21	+++	±	±	Once†
12	44	39	+++	±	±	0
13	11	11	++++	++	±	0
14	176	168	++++	++	2+	+
15	62	42	++++	±	3+	+
16	40	36	+++	±	1+	+
Average.....	30.4	24.4				
Median.....	13 to 15	11 to 12				

* Three months before death.

† Terminal.

cylindruria. His cases were those of tuberculosis of the bones and joints and of nonpulmonary tuberculosis.

CYLINDRURIA AND CYTOLOGY

The total duration of the cylindruria in each case is shown in table 4. Slight cylindruria was present from a minimum of one to a maximum of one hundred and seventy-six months, the average being thirty, and the median, from thirteen to fifteen months. Severe cylindruria occurred from a minimum of one to a maximum of one hundred and sixty-eight months, the average being twenty-four, and the median, from eleven to twelve months. This corresponds closely to the periods of slight and severe albuminuria. With the exception of case 7, the predominating type of cast was the hyaline variety, with from a few

to many fine droplets of fat. In a few cases typical fatty casts were seen. While we did not employ a "polarization" attachment on our microscope, we believe that one can distinguish the droplet of fat from the fine brown granule by manipulation of the light. A marked increase in the light makes the droplet of fat appear more opaque or black, while it causes the fine brown granule to become more or less invisible. This difference is more perceptible under low power than under high power magnification. The cast appears studded with black dots the size of pinpoints if droplets of fat are fairly abundant. When granular casts were present they were predominantly of the fine brown granular variety. Restriction of fluids after 6 p. m. increases the number of casts in the morning specimen.

The small round cell of the renal epithelium studded with droplets of fat and free droplets of fat were also frequently seen. In 7 cases (1, 4, 6, 7, 14, 15 and 16) pus in the sediment was present in quantity graded from one plus to four plus (one plus being from five to fifteen cells per high power field in centrifugated specimens). The first 4 patients were females, and the specimens were voided ones. Vaginal contamination is a possibility in all. Patients 10 and 11 showed red blood cells in one specimen only. Five patients (3, 7, 14, 15 and 16) more or less constantly showed a small number of red blood cells. The last 3 (14, 15 and 16) had hypertension and renal insufficiency.

In the majority of cases the urinary sediments showed the following: (1) from a few to many hyaline casts, with a varying number of fine droplets of fat; (2) a few fine brown granular casts; (3) a few white blood cells; (4) no red blood cells.

SPECIFIC GRAVITY OF THE URINE

The urinary observations just reported were on morning specimens. The sanatorium routine calls for examination of the urine once every three months. In order to obtain a normal average specific gravity, we took the first four specimens during the first year of residence of 50 consecutive living patients and of 20 patients with fatal cases in which there were no renal complications. The specimens were taken to cover every month of the year in patients in all stages of tuberculosis. The average specific gravity in 200 specimens from living patients and 80 specimens from patients with fatal cases was in both instances 1.0175 plus. We have, therefore, taken 1.018 as the average normal specific gravity of the morning specimen of urine in tuberculous patients under the sanatorium routine. Compared with this figure, the average specific gravity in our cases after the onset of renal amyloidosis is 1.014. The individual averages are shown in the chart listing the specific gravity in all the cases.

Probably the most constant and outstanding laboratory finding in these cases of renal amyloidosis is the urine of low specific gravity. In many instances the urinary pigments appear to be well excreted. The urine is dark, and the appearance suggests concentrated urine, but the specific gravity is found to be remarkably low.

Ten patients (1, 4, 5, 6, 7, 8, 11, 12, 13 and 15) showed consistently low readings for specific gravity. The last patient for eight and one half years after the onset of albuminuria did not pass a single specimen with a normal specific gravity (graphic chart for case 15). Four other patients (2, 3, 9 and 16) had only one normal specimen each of a total of thirty-two specimens examined (minimum, four specimens; maximum, eleven specimens, for individual cases). Patient 7 had two specimens with a normal specific gravity, of eight specimens examined. Patient 14 (chart for case 14) showed a specific gravity of unusual interest. For a period of four and one half years while cylindruria alone was present he secreted urine with a specific gravity at or above the normal line. For six years following the onset of albuminuria the specific gravity was at or usually below the normal line. For the last five years it was always below the normal line.

In one patient only (10) was the ability to secrete urine of normal specific gravity retained (graphic chart for case 10). This patient died of pneumonia four months after the onset of renal amyloidosis. His kidneys showed a very small amount of amyloid change. His ability to secrete urine of high specific gravity may be attributed to the small amount of damage to the medulla and to the fact that the convoluted tubules were intact. Kieffer¹⁰ stated that the specific gravity is usually high—at times, 1.035. The highest specific gravity in our series was 1.028 on only one occasion in the last case mentioned. Our experience is in accord with Holten's,¹³ who asserted that "hyposthenuria is the rule"—an observation which, according to his statement, was overlooked by Strauss and Volhard.

RENAL FUNCTION

Six patients had Volhard secretion and concentration tests. In only 1 case (13, on second examination) was the four hour output normal. Three patients showed essentially normal dilution. The ability to concentrate was impaired in all. The maximum concentration was 1.022 in case 16.

Nine patients were given the standard two hour and ten minute phenolsulphonphthalein test, with a normal result in case 2 (an output of 70 per cent) and case 13 (an output of 57.5 per cent, first test). In only 1 case was the output markedly lowered, namely in case 15 (an output of 22 per cent).

In all but 1 case (3) was the nonprotein nitrogen of the blood determined during the renal amyloidosis. Only 3 patients (12, 14 and 15) showed a significant degree of retention of nitrogen. In these the maximum nonprotein nitrogen was 174, 60 and 72 mg. per one hundred cubic centimeters of whole blood, respectively. In 2 other cases (10 and 13) the maximum figures were 43 and 46 mg., respectively. In the remaining cases the nonprotein nitrogen was normal, but in cases 4, 7, 10, 11 and 16 the interval (over three months) at which the

TABLE 5.—*Results of Renal Function Tests*

Case	Volhard Test			Output of Phenolsulphonphthalein in 2 Hours and 10 Minutes, Percentage	Nonprotein Nitrogen	
	Total 4 Hour Output, Percentage	Maximum Dilution	Maximum Concentration*		Mg.	Time Before Death
1	33	1 month
2	52	1.002	1.014	70.0	24	2 months
					35	1½ months
					24	½ month
3	
4	28	9 months
5	28	9 months
					31	½ month
6	45.0	33	1 week
7	40.0	34	14 months
					31	9 months
8	50	1.002	1.012	47.5	27	1½ months
9	29	3 months
10	43	5 years
11	40.0	31	16 months
12	39	2 years
					160	4 days
					174	1 day
13	50	1.004	1.012	57.5	29	8 months
	95	1.007	1.014	37.5	36	2 months
					46	1 month
14	64	1.002	1.021	45.0	33	6 years, 10 months
	49	1.003	1.017	40.0	34	4 years
					33	2 years, 10 months
					60	10 months
					50	7 months
15	72	1.005	1.010	22.0	41	39 months
					72	10 days
16	42	1.005	1.022	45.0	32	34 months
Normal....	80 to 100	1.001 to 1.002	1.028 to 1.032	55 to 70	30 to 35	

* Concentrations from 1.020 to 1.026 indicate moderate impairment, and those from 1.010 to 1.020, marked impairment.

nonprotein nitrogen was estimated was too long before death to enable one to state that renal insufficiency did not develop. At postmortem examination patients 10, 11, 12, 13, 14, 15 and 16 showed evidence of chronic nephritis. The results of the renal function tests are shown in table 5.

BLOOD PRESSURE

From one to several blood pressure readings were obtained in all the cases after the onset of renal amyloidosis (table 6). Normal blood pressure or hypotension was the usual finding. However, low blood pressure readings are common among our patients at the sanatorium. Patients 1 to 10, inclusive, had a low or normal blood pressure. It is

possible that hypertension may have developed in patients 4, 5 and 7 in the interval between the last reading (nine, nine and eleven and one-half

TABLE 6.—*Blood Pressure*

Case	On Admission		During Residence		Final Reading		
	Date	Blood Pressure	Date	Blood Pressure	Date	Blood Pressure	Time Before Death
		Sys.-Diastolic		Sys.-Diastolic		Sys.-Diastolic	
1	Dec. 5, 1924	100/ 66	July 9, 1927	100/ 60	Aug. 1930	104/ 70	1 month
2	July 2, 1925		March 16, 1928	92/ 80	March 29, 1928	70/ 50	4 days
			March 17, 1928	118/ 88			
			March 19, 1928	104/ 90			
			March 20, 1928	112/ 88			
			March 21, 1928	112/ 88			
3	Dec. 31, 1926	104/ 64	July 1928	100/ 66	2 months
4	Dec. 8, 1929	108/ 72	Sept. 1930	102/ 62	Oct. 30, 1930	90/ 70	9 months
			Oct. 16, 1930	108/ 70			
			Oct. 23, 1930	104/ 72			
5	Aug. 13, 1926	108/ 48	Nov. 7, 1930	104/ 64	9 months
	June 7, 1929	106/ 50					
6	May 18, 1928	125/ 78	July 26, 1928	100/ 60	1 day
7	Oct. 22, 1930	95/ 70	March 28, 1931	102/ 68	11½ months
8	Aug. 21, 1929	102/ 66	Oct. 18, 1930	102/ 74	Nov. 13, 1930	108/ 80	2 months
			Oct. 30, 1930	100/ 65			
			Nov. 6, 1930	96/ 70			
9	June 4, 1928	110/ 85	Jan. 24, 1931	108/ 65	3 months
10	Feb. 27, 1918	April 23, 1924	110/ 80	May 15, 1930	118/ 80	3 months
			Feb. 27, 1930	104/ 75			
			Feb. 27, 1930	120/ 80			
			March 6, 1930	104/ 78			
			March 13, 1930	108/ 80			
			March 20, 1930	108/ 80			
11	Nov. 21, 1929	120/ 72	Sept. 6, 1930	138/ 100	Nov. 13, 1930	116/ 92	16 months
			Oct. 30, 1930	115/ 96			
12	Aug. 30, 1924	118/ 74	Nov. 6, 1930	126/ 88	April 10, 1930	174/ 92	6 months
			Oct. 18, 1928	136/ 80			
			Oct. 25, 1928	138/ 88			
			Nov. 1, 1928	136/ 76			
			March 5, 1929	128/ 82			
			July 19, 1929	142/ 82			
			April 2, 1930	180/ 100			
13	Dec. 26, 1925	148/ 90	Jan. 1, 1926	125/ 90	Nov. 22, 1928	135/ 94	1 month
			Oct. 10, 1928	134/ 90			
14	April 10, 1917	Jan. 3, 1922	130/ 80	May 29, 1932	194/ 120	5 months
			Feb. 16, 1922	128/ 65			
			Dec. 29, 1925	140/ 98			
			Oct. 18, 1928	228/ 122			
			Oct. 19, 1928	226/ 122			
			Oct. 20, 1928	220/ 120			
			Oct. 16, 1929	204/ 130			
			March 3, 1930	194/ 120			
			July 3, 1930	200/ 130			
			Dec. 6, 1930	214/ 128			
			March 11, 1931	242/ 136			
			May 15, 1931	242/ 140			
			April 4, 1932	196/ 114			
15	July 25, 1923	108/ 80	Jan. 1, 1926	125/ 67	March 9, 1933	108/ 62	½ month
	Dec. 12, 1924	106/ 75	Oct. 10, 1928	120/ 78			
			Feb. 4, 1930	150/ 90			
			Feb. 11, 1930	146/ 88			
			Feb. 18, 1930	134/ 90			
			Dec. 6, 1932	136/ 74			
16	July 20, 1929	140/ 88	Feb. 4, 1930	162/ 110	Nov. 24, 1932	178/ 120	½ month
			Feb. 11, 1930	134/ 90			
			Feb. 18, 1930	154/ 98			

months, respectively) and death, although we do not consider it likely, since no renal vascular sclerosis was noted at autopsy. Patient 11 had a slightly elevated systolic and diastolic blood pressure in one reading and a slightly elevated diastolic and low pulse pressure in all the readings

except that taken on admission. His last reading (systolic, 116; diastolic, 92) was taken sixteen months before death. At that time the output of phenolsulphonphthalein was 40 per cent, and the nonprotein nitrogen, 31 mg. However, it is likely that a terminal rise of the blood pressure occurred, since at postmortem examination the glomerular lesion of chronic nephritis was present. Patient 12 showed a moderate grade of hypertension while under observation for renal amyloidosis. He had marked retention of nitrogen. At postmortem examination the kidneys showed arteriosclerosis and chronic nephritis. In patient 13 the condition might be termed latent hypertension. Renal amyloidosis did not appear to influence his blood pressure. He had a slight elevation of the nonprotein nitrogen one month before death. At postmortem examination the glomerular lesion of chronic nephritis was present. Patient 14 had marked and prolonged hypertension, the first evidence of which occurred four years after the onset of renal amyloidosis. Because of the high blood pressure and the good renal function as to the elimination of nitrogen during the period from eight to three years before death, we considered it highly probable that this patient had two conditions—renal amyloidosis and primary arterial hypertension. At postmortem examination marked arteriosclerosis and arteriolosclerosis and chronic nephritis were present. Patient 15 showed a slight degree of hypertension after the onset of renal amyloidosis. The blood pressure became subnormal two weeks before death. Postmortem examination showed arteriosclerosis and chronic nephritis. Patient 16 had a slightly elevated blood pressure on admission. Moderate hypertension developed. At postmortem examination arteriosclerosis and chronic nephritis were present. The 6 patients showing an elevated blood pressure were all males, and the ages at which the elevated blood pressures were first recorded were 32, 44, 46, 55, 55 and 69 years. From the evidence presented, it appears that hypertension occupies an inconspicuous position in the clinical picture of renal amyloidosis. It may be incidental rather than related to cause or effect.

EXAMINATION OF THE EYEGROUNDS

Examination of the eyegrounds was omitted in case 10. In 8 cases (1, 2, 4, 5, 6, 7, 8 and 9) the disks and retinas were normal, and there were no detectable vascular changes. Patient 3 showed a slight variation in the lumen of one inferior temporal artery. In case 13 one inferior temporal artery had a burnished appearance, suggesting early copper wire artery. In case 15 the arteries showed slight narrowing, and the choroidal vessels were slightly prominent. There was the "pepper and salt" fundus in both macular regions. In these 3 cases the vascular changes were so slight that they must be considered questionable. In

case 11 the arteries showed slight dulling of the light reflex, with slight narrowing and irregularity of the lumen. We consider these changes indicative of early retinal arteriosclerosis. Patient 12 showed slight increased vascularity of the disks, marked tortuosity of vessels, an increased light reflex (early copper wire artery) and moderate arterio-venous compression; in case 16 there were a moderately increased light reflex and irregularity of the lumen of the arteries, with slight arterio-venous compression. We consider that these 2 patients showed moderate retinal arteriolosclerosis. In case 14 the arteries showed marked irregularity and narrowing of the lumen of the arteries. Some were almost obliterated. There was slight compression at several arterio-venous crossings. This patient had marked retinal arteriolosclerosis. Retinal hemorrhages and retinitis were absent in all the patients examined. The findings just mentioned would indicate that the statements made concerning hypertension and renal amyloidosis apply also to retinal arteriolosclerosis and retinitis.

PHYSICAL FINDINGS

Certain relevant physical findings are shown in table 7.

Ten patients showed from slight to moderate pallor of the skin.

A very slight to marked edema was present in 5 cases. This was found at the time of the special physical examination, which was usually made within from one to three months after the onset of renal amyloidosis. In 2 of these cases the edema is recorded as being very slight. Edema, as noted at postmortem examination, was generalized in 6 cases. In 3 cases (12, 15 and 16) it was recorded as very slight; in 2 cases (7 and 14), as moderate, and in 1 case (2) as marked. Localized edema, particularly of the feet and hands, was slight in 3 cases (1, 3 and 8), moderate in 5 (4, 5, 6, 9 and 11) and absent in 2 (10 and 13). Simon¹¹ found edema in 11 of 45 cases, and initial edema was present in 6 of 30 cases observed from the beginning. He stated that in a large number of cases there is no edema present, except terminal edema. Holten¹³ stated that initial edema such as that seen in ordinary nephritis is not present. In 13 of 30 of his cases there was no edema, and in only 3 cases was edema present that was not terminal. Our observations that the initial edema of ordinary nephritis is not present in renal amyloidosis are in accord with Holten's. When edema is present in the early stage of renal amyloidosis it is more insidious in its onset. One of our patients (12) had marked albuminuria for four years and at postmortem examination showed only a very slight generalized edema, and another patient (13) had severe albuminuria for nine months and no edema. We cannot find any agreement in the amount of albuminuria and edema in our series. It is possible that our patients were protected against deple-

TABLE 7.—Physical Findings and Postmortem Weights*

Case	Sex	Pallor	Edema		Peripheral Arterio-sclerosis	Liver		Spleen		Heart		Time of Physical Examination, Months Before Death
			Grade	Location		Gm. Below Costal Margin	Postmortem Weight, Gm.	Gm. Below Costal Margin	Postmortem Weight, Gm.	Cardio-thoracic Index	Postmortem Weight, Gm.	
1	F	2+	1+	Ankles; legs	3+	Enlarged	1,560	Enlarged	270	40	230	2
2	M	2+	3+	Legs; abdomen	1+	Not palpable	2,015	Not palpable	241	39	212	1
3	M	2+	0	..	0	3.0	3,405	0	475	35	210	4
4	F	0	0	..	0	0	2,666	0	340	41	146	12
5	M	2+	0	..	2+	8.0	3,070	0	246	40	163	10
6	F	1+	0	..	0	5.0	3,950	2	524	41	405	1
7	F	2+	2+	Face	3+	3.5	2,440	2	650	41	155	13
8	F	1+	0	..	0	3.0	2,750	0	245	34	160	3
9	F	2+	0	..	0	8.0	2,835†	6	300	41	197	6
10	M	1,450	..	206	38	417	..
11	M	0	0	..	3+	0	2,325	0	268	40	228	20
12	M	0	0	..	2+	0	1,967	0	108	40	588	7
13	M	0	0	..	3+	0	1,200	0	240	33	297	2
14	M	2+	2+ to 3+	Face; legs	3+	0	1,902	0	215	..	457	6
15	M	2+	1+	Legs	2+	0	2,800	4	543	43	335	42
16	M	0	0	..	2+	0	2,085	2	260	44	580	34
Average.....									320.7		298.8	

* The normal weight of the liver was considered to be 1,800 Gm. for males and 1,500 Gm. for females; 2,250 Gm. represents a 25 per cent increase for males, and 1,875 Gm., a 25 per cent increase for females. The normal weight of the spleen was considered to be 150 Gm. for both males and females; 270 Gm. represents an 80 per cent increase.

† Our original records show 1,835 grams as the weight of the liver in this case. As the liver is described as "firm and heavy" on gross examination, we believe that the 2 Kg. weight on the scales was misread as 1 Kg.

tion of plasma protein and edema because they were kept on a general diet with adequate protein as long as their general condition permitted.

Peripheral arteriosclerosis was an inconstant finding. When present, it could not be reconciled with other clinical features of renal amyloidosis.

The clinical estimate of the enlargement of liver and spleen, together with the postmortem weights, are given in table 7. In the 9 patients examined six months or less before death the clinician's estimate of the size of the liver and spleen was 100 per cent correct when compared with the postmortem weights. Patient 10 was not examined. In the remaining 6 patients, who were examined more than six months before death, the estimate was correct for 3. We assume that a 25 per cent increase in the size of the liver and an 80 per cent increase in the size of the spleen is necessary before enlargement of these organs can be positively established by physical diagnostic methods. These figures correspond closely with the standards of Barron and Litman,¹⁵ who consider livers weighing 2,200 Gm. or more and spleens weighing 300 Gm. or more as hypertrophied and enlargement demonstrable by palpation. Our figures are 2,250 and 1,875 Gm., respectively, for the weight of the liver in the male and female and 270 Gm. for the weight of the spleen in both sexes, using as a basis for calculation 1,800 Gm. as the normal weight of the liver for males and 1,500 Gm. as the normal weight for females and 150 Gm. as the normal weight of the spleen for both sexes. These figures closely approximate the normal figures given by Boyd.¹⁶

On this basis, if enlargement of the liver had been made a requirement for a positive diagnosis of renal amyloidosis, the percentage of diagnostic error would have been 44 per cent. If enlargement of the spleen had been made a diagnostic requirement, the percentage of diagnostic error would have been 56 per cent. If the usual textbook diagnostic triad of chronic suppuration, enlarged liver and spleen and albuminuria had been insisted on, the diagnostic accuracy would have been 25 per cent. In the findings just described we have not considered the cavity of pulmonary tuberculosis as a chronic suppurating focus. On the basis of the postmortem weights, only 2 patients (10 and 13) failed to show some enlargement of the liver, and only 1 (12), enlargement of spleen.

The cardiothoracic index did not prove to be a reliable indicator of the size of the heart, when compared with the postmortem weights. This is due in part to the fact that in far advanced and fibroid tuberculosis and in patients receiving pneumothorax treatments the cardiothoracic

15. Barron, M., and Litman, A. B.: Importance of Hepatomegaly and Splenomegaly in Differential Diagnosis, *Arch. Int. Med.* **50**:240 (Aug.) 1932.

16. Boyd, E.: Normal Variability in Weight of the Adult Human Liver and Spleen, *Arch. Path.* **16**:350 (Sept.) 1933.

index is difficult to determine with accuracy. Six patients (6, 10, 12, 14, 15 and 16) had hearts above normal weight at postmortem examination (325 Gm., males; 250 Gm., females). Of these, the last 5 had renal insufficiency, and the last 4 had hypertension. Renal amyloidosis did not appear to favor cardiac enlargement in our series. In contrast, in 9 cases the heart was considerably under normal weight.

The congo red test according to the technic of Bennhold was performed in 6 cases (6, 8, 9, 11, 14 and 15).¹⁷ The percentage of disappearance of the dye was 100, 40, 39, 90, 90 and 100, respectively. Patients 8 and 11, with a disappearance of 40 and 39 per cent, respectively (a 25 to 50 per cent doubtful range), had enlargement of both the liver and the spleen, while patient 14, with 90 per cent disappearance, had only very slight enlargement of the liver and spleen at postmortem examination (the liver weighed 1,902 Gm.; the spleen, 215 Gm.). While the congo red test is helpful in the diagnosis of amyloidosis, our experience with it in this series and in other cases leads us to believe that there is considerable variability of response. We agree with Rosenblatt¹⁴ that in patients with chronic pulmonary tuberculosis the diagnosis of renal amyloidosis may be made with relative certainty without the congo red test. We performed the test only in cases in which the diagnosis of renal amyloidosis had been made. It is admitted, however, that in doubtful cases, such as differentiation from other types of nephritis and general amyloidosis without albuminuria and cylindruria, a positive result of the congo red test should carry considerable weight in the diagnosis.

Three patients (6, 12 and 15) had positive Wassermann reactions on admission. Patient 6 had one course of neoarsphenamine and mercury, which produced a negative serologic reaction. She showed a negative reaction on readmission in 1928. Patient 12 had a positive Wassermann reaction on second admission (no test was carried out on first admission), and it remained positive for three years. He had prolonged treatment with arsphenamine, mercury and bismuth. His serologic reaction became negative four years after the beginning of treatment. Patient 15 had two positive serologic reactions on admission. Four reactions over a seven year period were negative. In the aforementioned cases there were no clinical or postmortem evidences of syphilis. The serologic reaction in the remaining cases was negative.

PATHOLOGIC EXAMINATION

A careful search for evidence of amyloid degeneration was made in other body tissues. The tissues, in addition to gross examination with the iodine reaction, were also examined when stained by hematoxylin

17. Dr. George Fahr supplied the data for the last three cases.

and eosin and methyl violet. The distribution of amyloid in various organs as found at postmortem examination is shown in table 8. All the patients had amyloid in the kidneys, liver and spleen. In case 8 the

TABLE 8.—*Distribution of Amyloid as Noted at Postmortem Examination**

Case	Kidney	Liver	Spleen	Pancreas	Adrenals	Mesenteric Lymph Nodes	Retroperitoneal Lymph Nodes	Appendix	Tracheal Lymph Nodes	Thyroid	Small Intestine	Large Intestine
1	A	A	A	—	a	—	O	—	—	O	—	—
2	A	A	A	A	A	A	A	—	—	O	—	—
3	A	A	A	A	A	?	O	A	A	O	—	A
4	A	A	A	A	A	—	O	—	—	—	A	A
5	A	A	A	—	A	A	O	—	—	—	—	—
6	A	A	A	—	A	—	O	—	—	O	—	—
7	A	A	A	—	?	?	—	—	—	—	?	A
8	A	A	A	—	A	—	O	—	—	O	A	O
9	A	A	A	A	a	—	O	A	—	A	—	—
10	A	A	A	—	a	—	O	—	—	O	A	—
11	A	A	A	—	A	A	—	—	?	A	—	—
12	A	A	A	—	A	—	O	—	—	O	—	—
13	A	a	A	—	A	—	O	—	—	O	—	—
14	A	A	A	—	A	A	A	—	—	A	—	—
15	A	A	a	—	A	—	O	—	—	A	A†	—
16	A	A	A	—	A	—	O	—	—	?	—	—
Total Cases....	16	16	16	4	15	4	2	2	1	4	4	3

* A indicates amyloid; a, a small amount of amyloid; O, no tissue examined, and —, no amyloid.

† The pylorus.

TABLE 9.—*Distribution of Amyloid and Other Lesions in the Kidney*

Case	Weight of Kidney, Gm.	Amount of Amyloid				Thickened Bowman's Capsule	Tubules		Sclerosis		Infiltration
		Cortex		Medulla			Suppression, with Dilatation of Those Remaining	Epithelial Degeneration	Arteries	Arterioles	
		Glomeruli	Interstitial	Capillaries	Interstitial						
1	234	±	—	—	+	..	+	—	
2	515	++	+	+	±	..	+	—	
3	213	+	+	++	+	..	+	—	
4	268	++	±	+	±	+	..	—	
5	242	++	±	+	+	+	..	+	
6	427	++	+	+	—	..	++	?	..	+	
7	848*	±	+	—	++	..	++	—	..	+	
8	309	++	±	+	++	++	..	—	
9	315	++++	+	++	+++	+	++	—	..	+	
10	271	±	±	±	—	+	..	—	
11	326	++	+	+	++++	..	+	+	..	—	
12	276	+++	±	++	+++	++++	++	+	+	+	
13	330	+	+	+	—	+++	++	+	++	+	
14	415	++++	+	+++	+	+	++	+	++	+	
15	286	++++	++	+++	+++	++++	+++	+	++	+	
16	433	++++	+	+++	++	+	++	+	++	+	

* Enormous tuberculous abscess of the right kidney.

liver tissue was not examined microscopically, since inadvertently no liver tissue was saved, but amyloid was demonstrated macroscopically by the iodine test. Patient 13 showed only a very small amount in the liver, and patient 15, a small amount in the spleen. All but one patient showed amyloid in the adrenals. In 7 cases amyloid was present in some

portion of the gastro-intestinal tract. The abdominal lymph nodes, pancreas and thyroid showed amyloid with considerable frequency. Our results are in close accord with those of Rosenblatt.¹⁴

The weights of the kidney and the microscopic distribution of amyloid are given in table 9. When the degree and duration of albuminuria and cylindruria are compared with the amount and distribution of amyloid in the kidney, it is difficult to establish any definite correlation except to state that the patients showing the smallest amount of amyloid (1, 7 and 10) were those in whom the albuminuria and cylindruria were of short duration.

SUMMARY

1. The clinical course in 16 cases of renal amyloidosis in which amyloid deposits were demonstrated in microscopic section of kidney tissue by methyl violet staining at postmortem examination is presented.

2. If albuminuria and cylindruria appear in the course of advanced pulmonary tuberculosis complicated by a suppurative process, tuberculosis of the serous membranes, enteritis or any other major complication of tuberculosis or in tuberculosis of the osseous system, the diagnosis of renal amyloidosis may be entertained, with the expectation that further study will confirm it. If, associated with these changes, the liver and spleen are enlarged, the diagnosis may be considered reasonably well established. If the liver and spleen are not enlarged, the presence of edema, normal or low blood pressure, hyposthenuria, a normal output of dye, normal nonprotein nitrogen and normal eyegrounds support the diagnosis.

3. The clinical complication of tuberculosis occurring most often in association with renal amyloidosis is clinical enteritis (10 cases). The most common complication observed post mortem is tuberculous adenitis (12 cases). Tuberculous complications involving the alimentary tract and the serous membranes form two important groups.

4. In all but 2 cases it is possible to point out an unusual event in the clinical course of the disease that may have been the precipitating complication or factor in determining the onset of the renal lesion. The most prominent events in this probable relationship are clinical enteritis, pleural effusion, empyema, the institution of pneumothorax and other surgical procedures.

5. The average duration of albuminuria was thirty-three months; the median, from fifteen to sixteen months. The average duration of severe albuminuria was twenty-one months; the median, from nine to twelve months. Albuminuria preceded cylindruria in 6 instances.

6. The average duration of cylindruria was thirty months; the median, from thirteen to fifteen months. The average duration of

severe cylindruria was twenty-four months; the median, from eleven to twelve months. Cylindruria preceded albuminuria in 3 instances.

7. In ten patients the urine showed a consistently low specific gravity. In only 1 patient was the ability to secrete urine of normal specific gravity retained. The kidneys in this case showed probably the smallest amount of amyloid deposit present in the series.

8. A diminished four hour output and impaired concentration were the most constant findings in the renal function tests.

9. Our data make it appear that hypertension occupies an inconspicuous position in the clinical picture of renal amyloidosis. It may be incidental rather than related to cause and effect. Arteriolosclerosis of the retinal vessels and retinitis occupy a similarly inconspicuous place.

10. If the usual textbook 'triad' of the older clinicians of chronic suppuration, enlarged liver and spleen demonstrable by physical examination and albuminuria had been insisted on, the diagnostic error would have been 75 per cent.

(Charts and descriptions appear on following pages)

GRAPHIC CHARTS FOR EACH CASE SHOWING THE TIME RELATIONS OF
THE VARIOUS DIAGNOSTIC TESTS

The horizontal distance represents the length of time the patient was observed from first admission to death. The blank spaces bounded by dotted lines represent the time between discharge and readmission. The horizontal distance is marked by years and half years at the bottom of the chart; age is indicated at the top.

Elements of Urinalysis.—Some of the results of single tests are represented on a time grid.

Albumin.—This was determined by a qualitative test with saturated sodium chloride and 2 per cent solution of acetic acid to eliminate mucus in the precipitate.

Specific Gravity.—The ends of the bars represent the reading of the specific gravity. The bars are extended to the 1.018 reading to show the variation around this figure as a normal.

Volhard Test.—See table 5 for the actual values. The percentage of water excreted is represented by the black bar. The ends of a cross-hatched bar above it represent the maximum and minimum specific gravity for the test.

Casts.—The number of casts are shown by the height of the bar. White bars represent hyaline casts. Cross-hatching represents granular casts. The amount of the cross-hatching represents the proportion of granular casts to hyaline casts.

White Blood Cells.—The height of the bar represents the number of white blood cells in the sediment of the urine, as explained in the text.

Red Blood Cells.—The height of the bar represents the number of red blood cells in the sediment of the urine.

Nonprotein Nitrogen.—The actual values of the nonprotein nitrogen of the blood are given in table 5. The time when the determination was made and an approximate representation of its value is given in relation to a 30 mg. guide line.

Congo Red Test.—The percentage of dye that disappeared from the blood is indicated by the height of the bar.

Blood Pressure.—The ends of the vertical black bars represent the systolic and diastolic readings. The 120 and 80 mm. lines are used as guides. Table 6 gives the actual values.

Examination of the Eyegrounds.—The time of examination of the eyegrounds is represented by the tiny square on the base line. White squares represent normal findings; black squares represent pathologic findings.

Phenolsulphonphthalein Test.—The height of the bar represents the percentage excreted in two hours. See table 5.

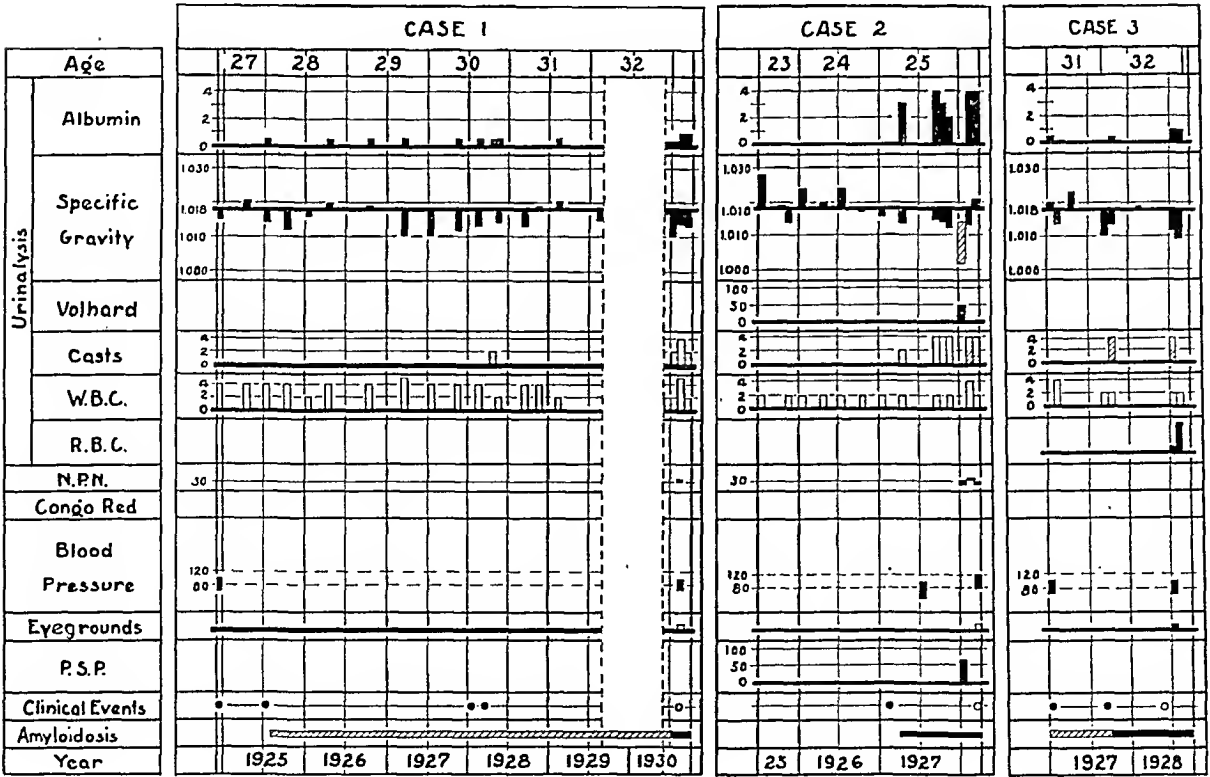
Clinical Events.—The black dots indicate the time of the various events listed in table 2. The white dots represent the time of the clinical examination for this study and the time when clinical amyloidosis was diagnosed.

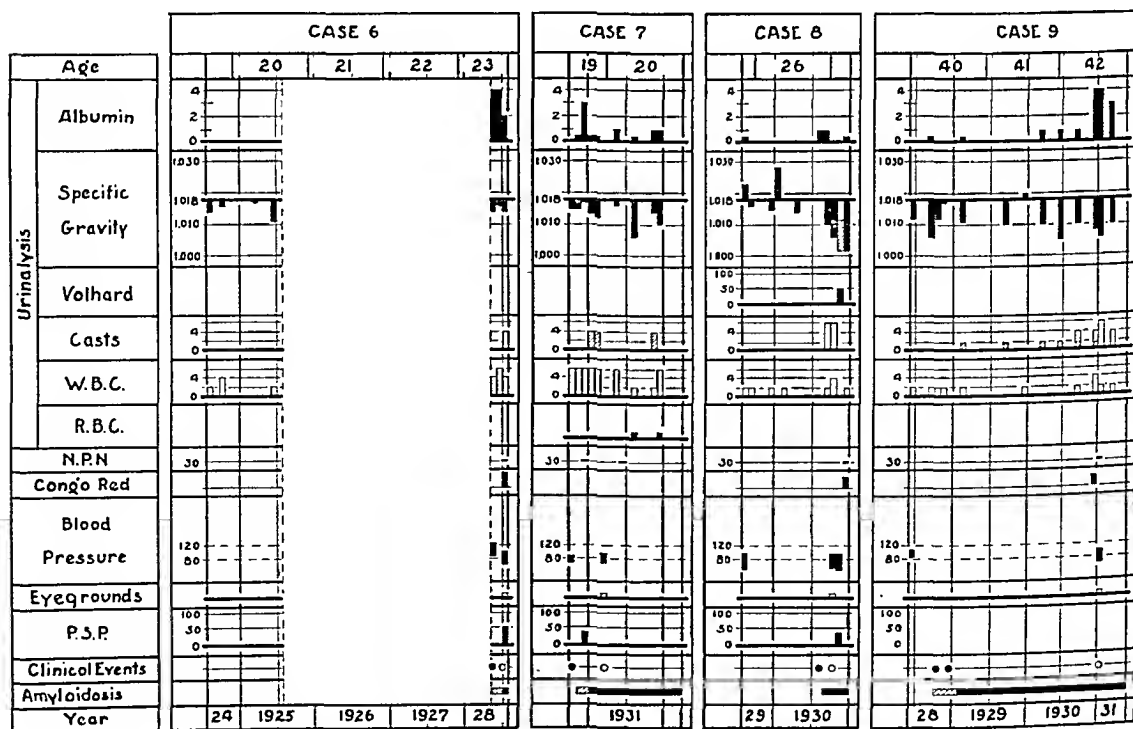
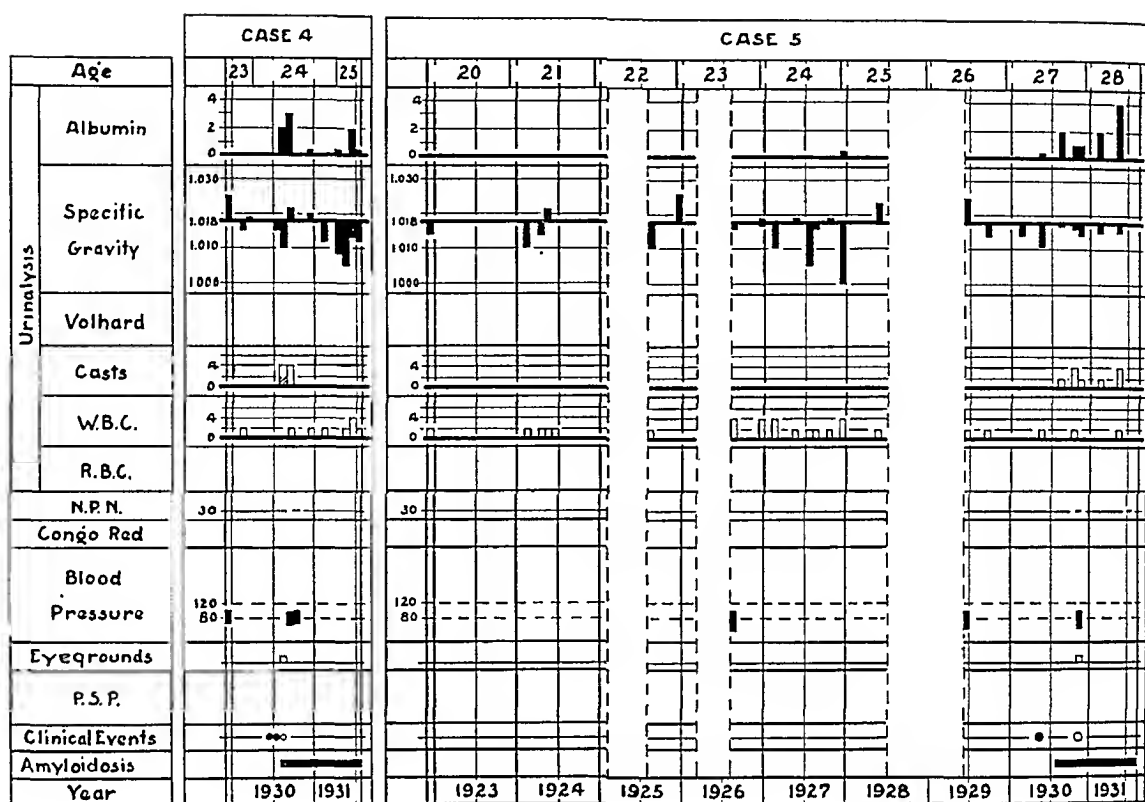
Amyloidosis.—The horizontal black bar represents the duration of clinical signs sufficiently definite to enable one to make a diagnosis of amyloidosis. It may be noted that in many of the cases the left end of the bar antedates the time when the clinical examination of the patient for this study was made. The cross-hatched bar represents the time during which amyloidosis of the kidneys was suspected but could not be definitely established.

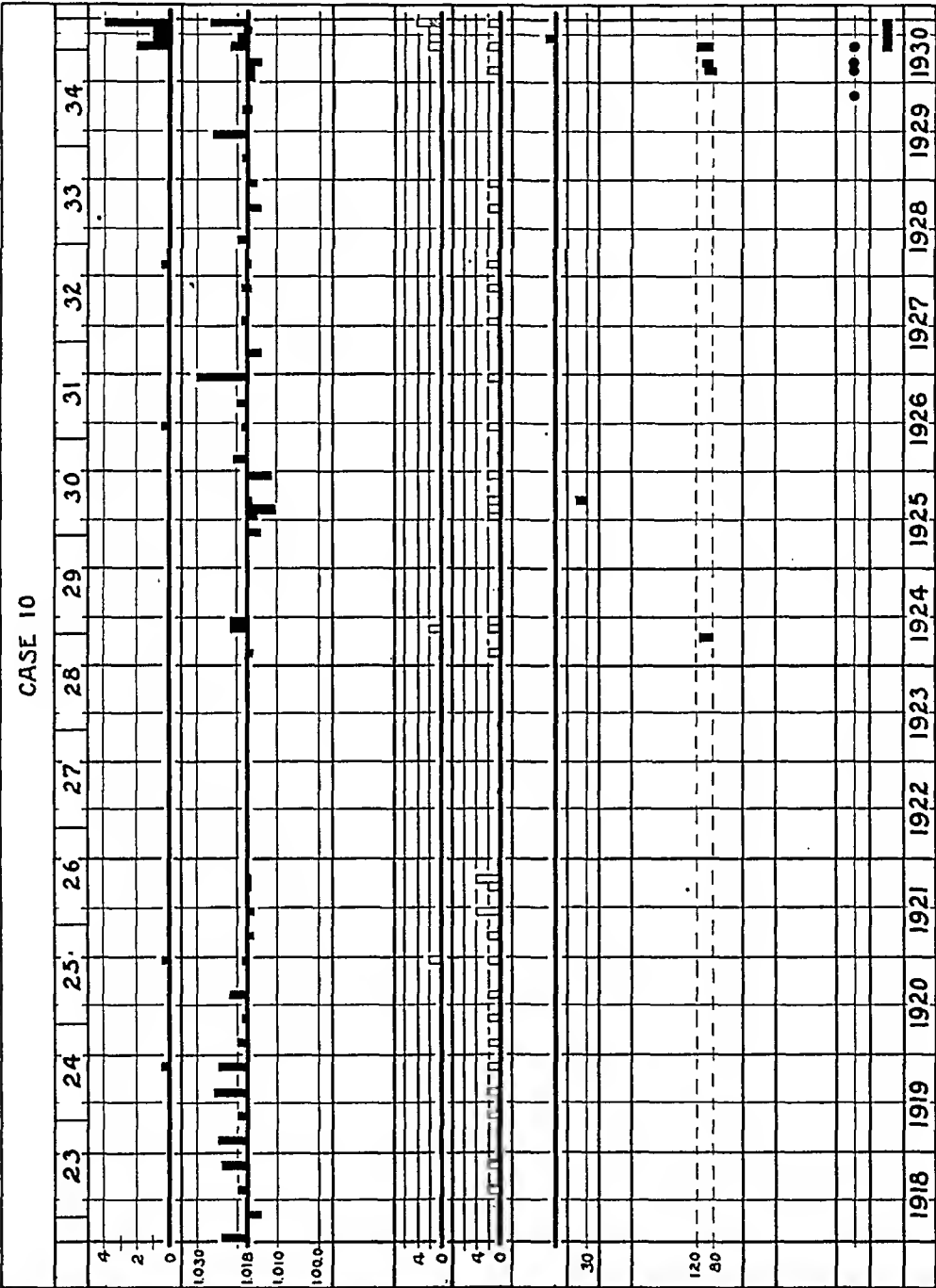
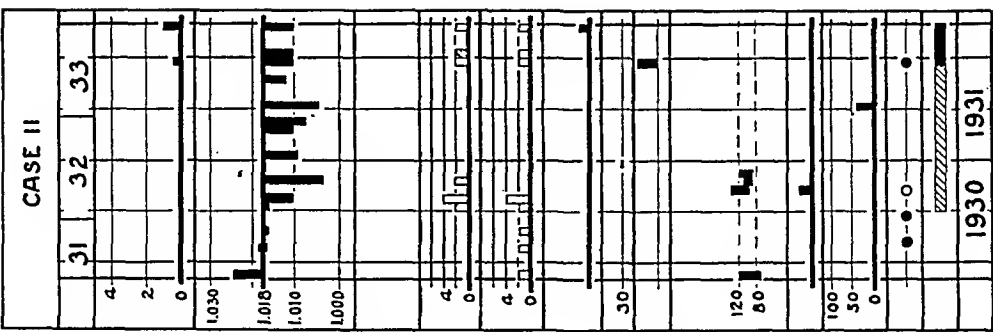
PHOTOMICROGRAPHS

The low power photomicrographs 1 to 16 correspond to the cases so numbered. They show representative fields of amyloid in the renal cortex in each case.

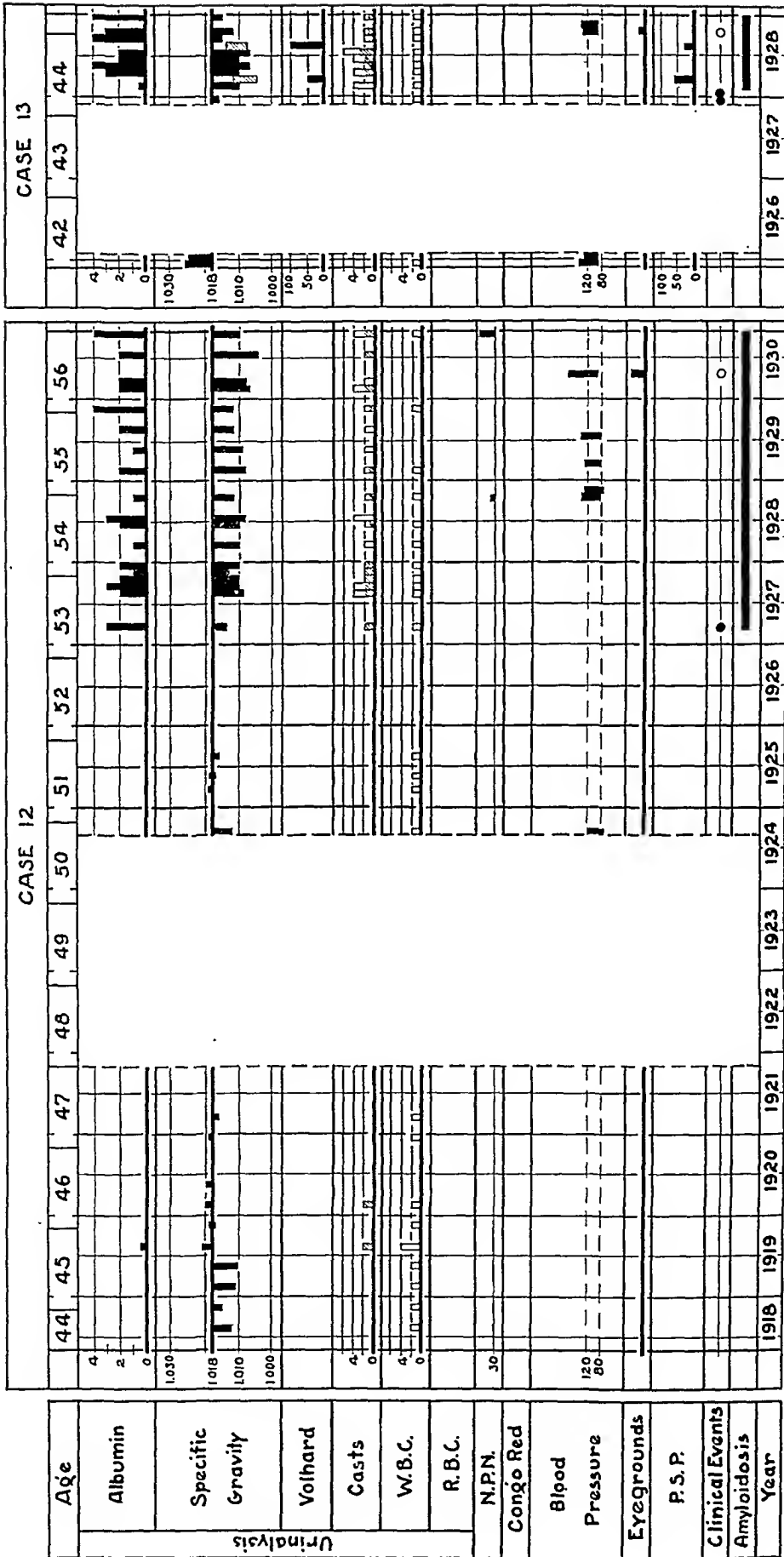
Average Specific Gravity of the Urine in Individual Cases																
Specific Gravity	Case Number															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1.025																
1.024																
1.023																
1.022																
1.021										■						
1.020																
1.019																
1.018																
1.017																
1.016	■	■			■											
1.015						■										
1.014																
1.013			■	■										■		
1.012							■									■
1.011									■			■	■		■	
1.010											■					
1.009																
1.008																
1.007								■								
1.006																
1.005																
No. Specimens	4	10	6	13	7	2	7	5	12	5	4	21	15	63	31	10



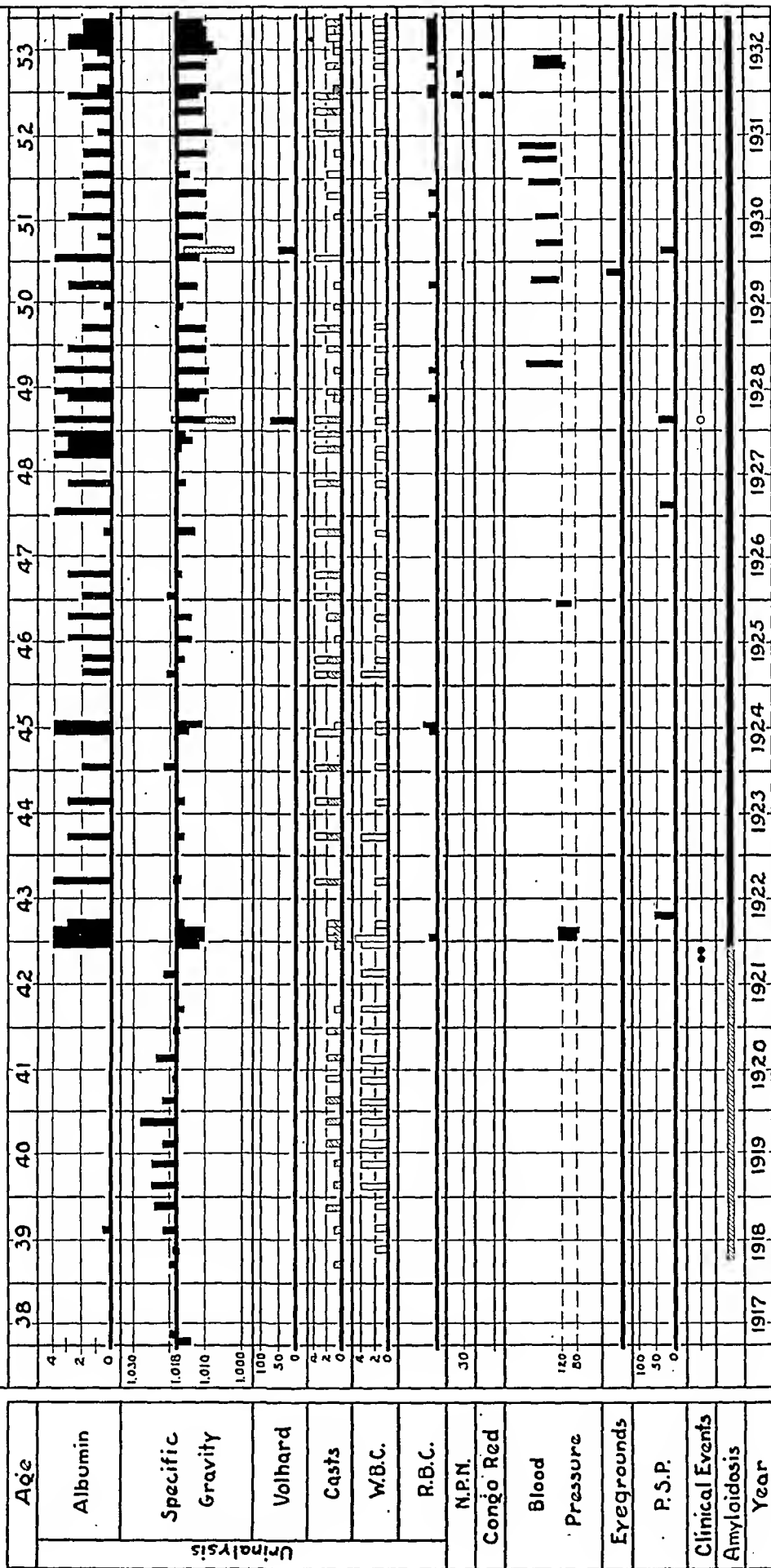




Age
Albumin
Specific Gravity
Volhard
Casts
W.B.C.
R.B.C.
N.P.N.
Congo Red
Blood Pressure
Eye grounds
P.S.P.
Clinical Events
Amyloidosis
Year

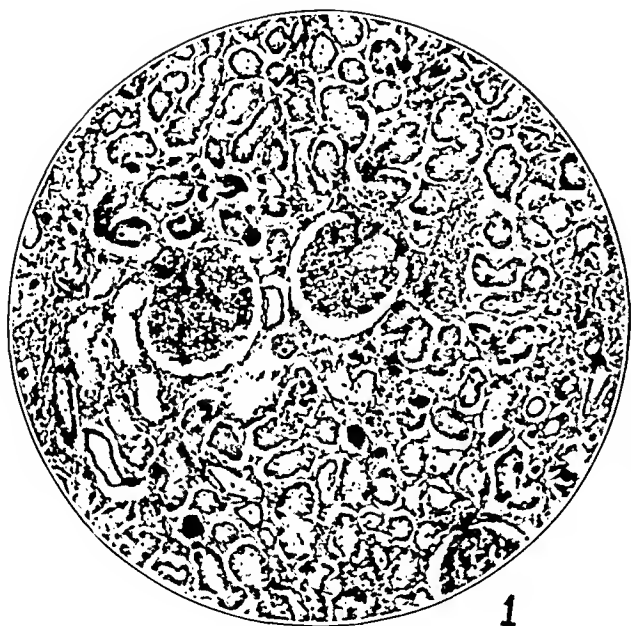


CASE 14



[illegible][illegible]

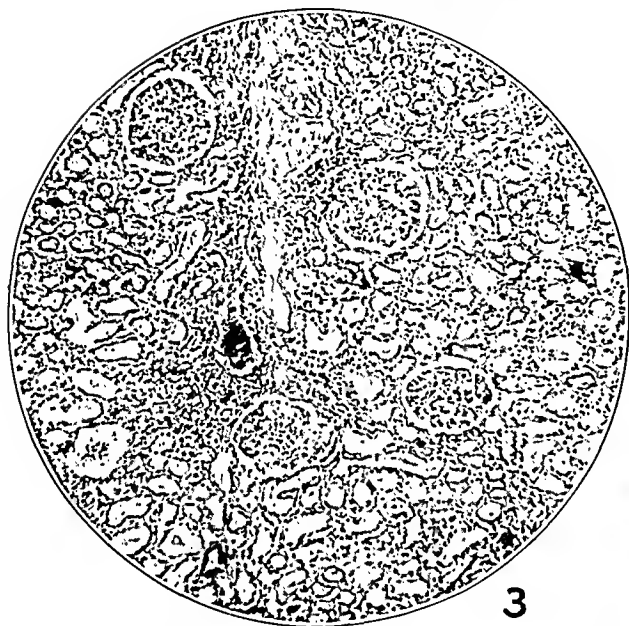
Age	
Albumin	
Specific Gravity	
Volhard	
Casts	
W.B.C.	
R.B.C.	
N.P.N.	
Congo Red	
Blood Pressure	
Eye grounds	
P.S.P.	
Clinical Events	
Amyloidosis	
Year	



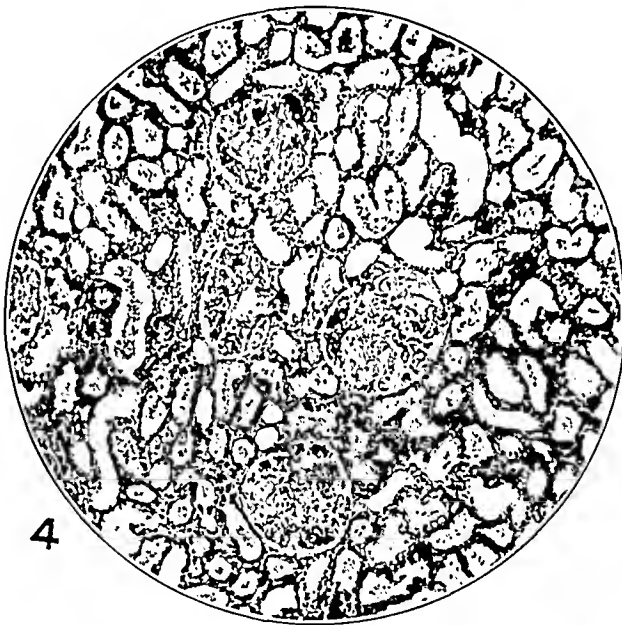
1



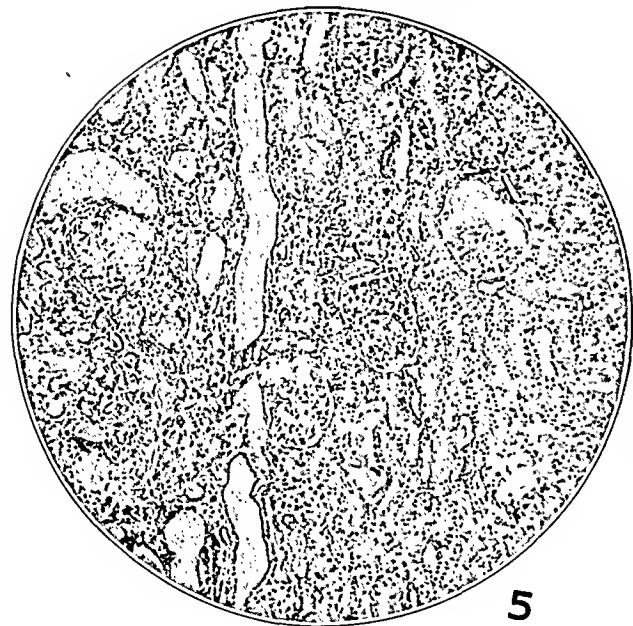
2



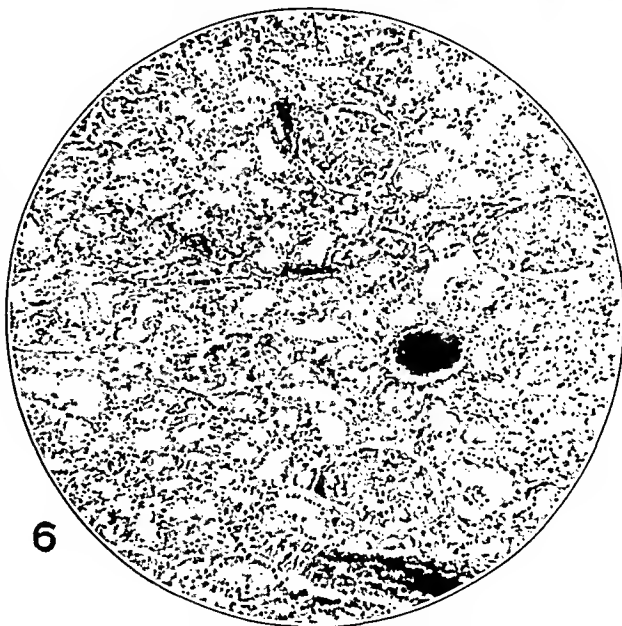
3



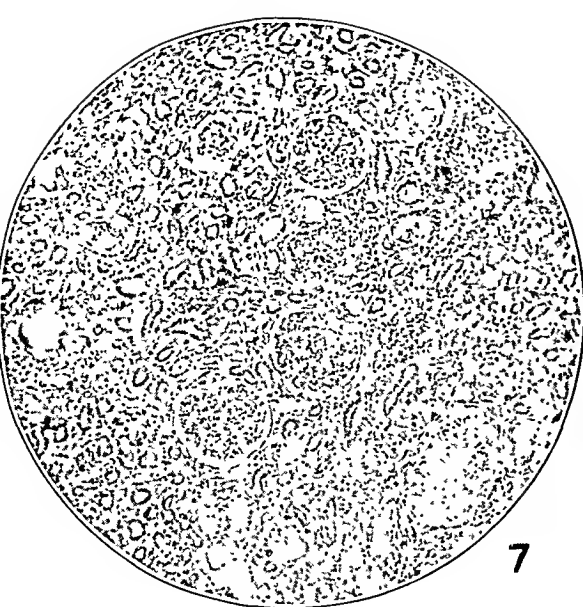
4



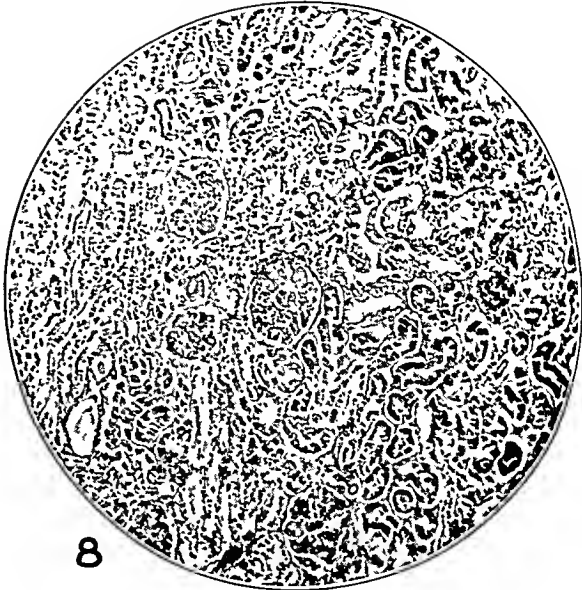
5



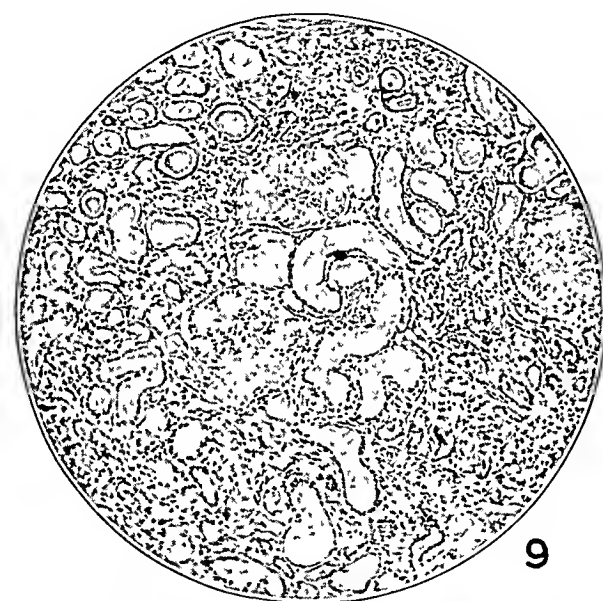
6



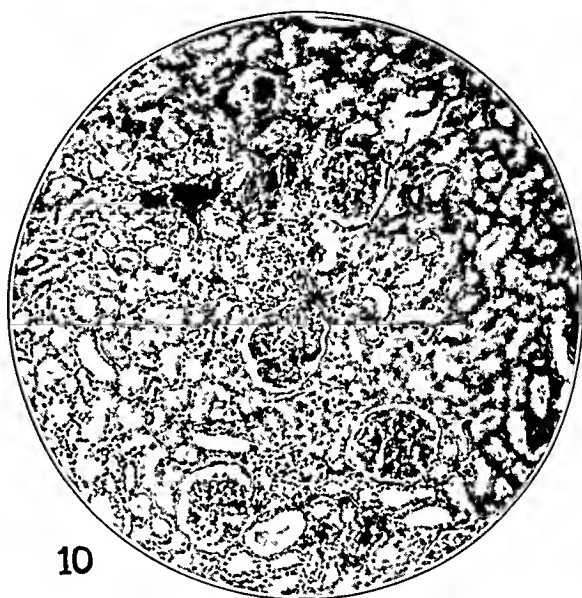
7



8



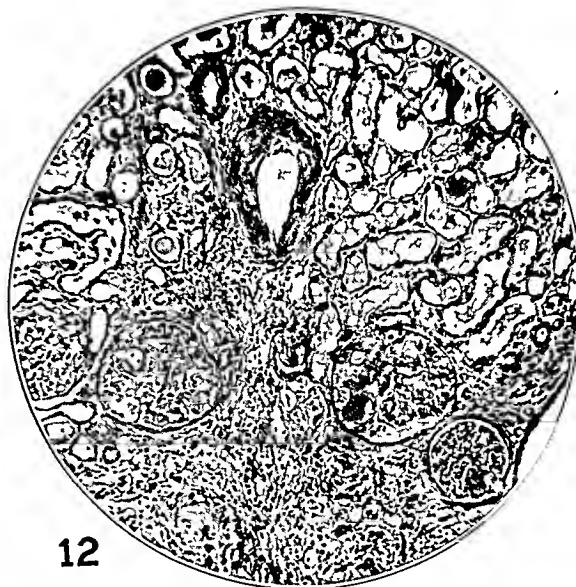
9



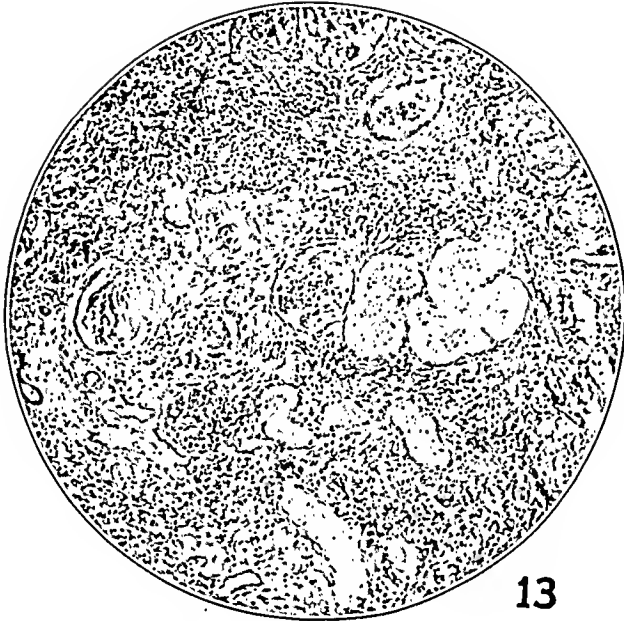
10



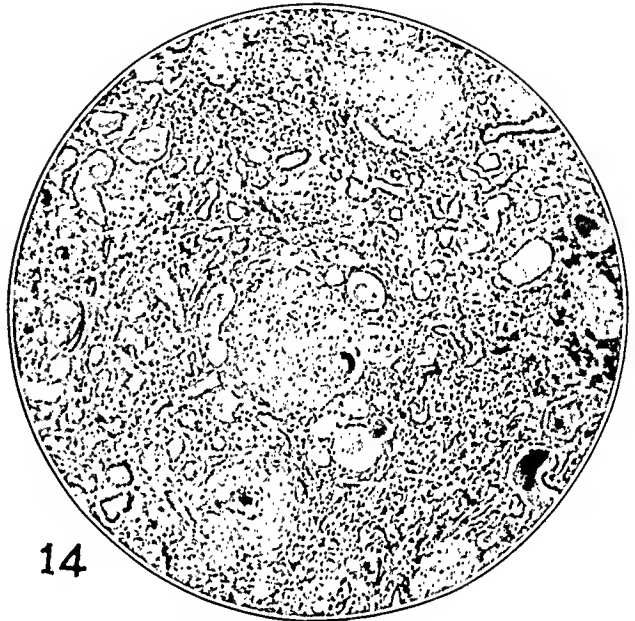
11



12



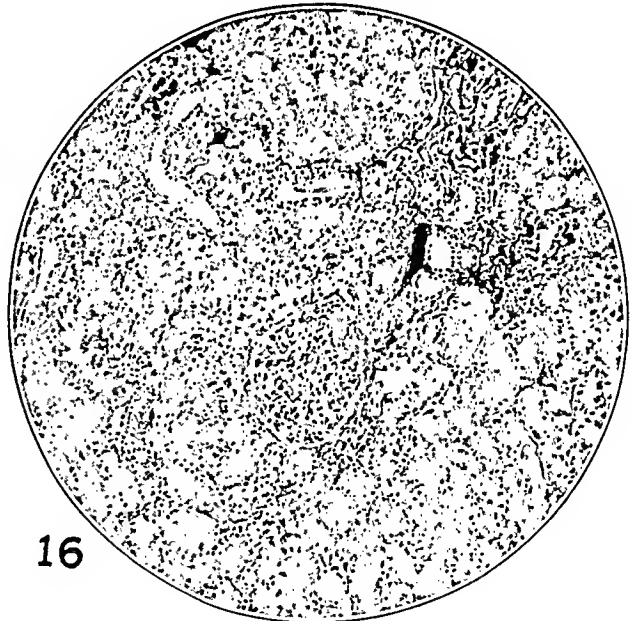
13



14



15



16

PATHOLOGY OF THE VESSELS OF THE PULMONARY CIRCULATION

PART IV

O. BRENNER, M.D., M.R.C.P.

Physician for Outpatients and Physician in Charge of the Cardiographic
Department, Queen's Hospital

BIRMINGHAM, ENGLAND

PRIMARY PULMONARY VASCULAR SCLEROSIS

In this rare condition there is sclerosis of the pulmonary arteries for no obvious reason (such as cardiac or pulmonary disease) as well as hypertrophy of the right but not the left side of the heart. Most of the patients die of heart failure. Hypertrophy of the right side of the heart, though not stressed in the definitions given in the literature, is particularly important. In the present series, 23 of 31 patients without cardiac or pulmonary disease showed pulmonary vascular sclerosis, but circulatory symptoms and hypertrophy of the right heart were present in only 1 patient, the only one in whom a diagnosis of primary sclerosis was justified. In many cases reported in the literature chronic pulmonary or cardiac disease was present or hypertrophy of the right heart was absent, so that those cases must be considered as spurious. The question may be clarified by describing 2 cases of the condition (1 of which is included among the 100 consecutive cases in the present series).

REPORT OF CASES

CASE 1.—*History and Course.*—D. D., a boy, was 11 years old at the time of death. He was apparently healthy at birth. He had an attack of influenza at the age of 3 years, and the tonsils were then removed. At 8 he had measles, the right antrum was opened and the appendix removed. At operation a condition of modified Hirschsprung disease was noted. After that there was some dyspnea on exertion with dizziness. The lips and cheeks had always been blue when the child was cold. In May 1929, at the age of 9, he had an attack of chickenpox, and after that the dyspnea and dizziness were more marked. Shortly afterward he had an attack of polio-encephalitis, with palatal and facial palsy, but recovery was satisfactory. In 1929 he had an operation for "anomalous bones in the feet." There was no history of rheumatism. He was examined at that time. The skin was pale, but the lips were bright red. The pulse rate was 90. The heart was not enlarged. There was a slight pulmonary systolic murmur, and the pulmonary second sound was accentuated. A roentgenogram showed that the heart was of normal size, with a prominent pulmonary artery. The electrocardiogram showed slight right

In this series of five papers the superior numbers refer to the bibliography which will be published in connection with the last paper. The superior letters refer to footnotes.

axis deviation. The diagnosis at that time was "effort syndrome, ? congenital cardiac disease." In the next two years he had several syncopal attacks, with drowsiness, cyanosis, muscular rigidity and incontinence, followed by vomiting. In January 1931 he had "grip" followed by otitis media and whooping cough. After that the dyspnea and tendency to cyanosis increased. Examination in June 1931, at the age of 11, revealed a good but deep color, a slightly enlarged heart and a slight harsh systolic pulmonary murmur. The pulmonary second sound was greatly accentuated and sometimes followed by a diastolic murmur. A roentgenogram showed that the heart was full-sized, with marked prominence and increased pulsation of the pulmonary artery and hilar shadows. The Wassermann reaction was negative. The electrocardiogram showed marked right axis deviation. The diagnosis was "patent ductus arteriosus, with some other defect also (?)."

In the next two months there was constantly increasing dyspnea on exertion, with slight cyanosis. Severe pain in the chest and down both arms also was felt after exertion. On Aug. 17, 1931, he had an attack of pain while being wheeled in a chair, and he died in a few minutes.

Gross Postmortem Examination.—Autopsy was limited to an examination of the thoracic organs. The body was that of a well developed and well nourished boy. There was no edema. The pleurae, thymus, bronchial lymph glands, larynx, trachea and main bronchi were normal. The lungs showed moderate congestion and edema of the lower but not the upper lobes. The pericardium was 12 cm. in transverse diameter and contained 75 cc. of serous fluid. The heart (weight, 305 Gm.) was enlarged, with marked dilatation and great hypertrophy of the right ventricle, which was 15 mm. thick at the conus and 6 mm. thick near the apex. Its columnae carneae were greatly hypertrophied. The left ventricle (fig. 21) was normal (from 9 to 12 mm. thick). The right auricle was not dilated or hypertrophied. The left auricle was small, and its wall was thin. The valves were normal apart from a patch of fatty degeneration on the aortic flap of the mitral valve. The coronary arteries showed a single small patch of early atheroma at the origin of the left main trunk. There was one patch of early atheroma in the descending aorta. Seven centimeters above the aortic cusps there was a small blind pit, proximal to which there was a fold of intima 1 cm. long and concave upward. The ductus arteriosus was closed. The stem and right and left branches of the pulmonary artery were not dilated (circumference of the stem, 5.9 cm. [aorta, 4.9 cm.]; circumferences at the hili, 3.7 cm.), but their walls were thickened, and their intima as well as that of the main intrapulmonary branches was thickened and pitted. In the branches below the second order the intima rapidly thinned and became translucent. Two small, raised, yellow, atheromatous patches were present in the stem just above the cusps, and a few similar patches were present in the branches of the first and second orders. Vessels with a diameter as small as 3 or 4 mm. stood out rigid and gaping on the cut surface of the lung. The four pulmonary veins entering the left auricle were thin-walled and narrow, their circumferences ranging from 0.9 to 2.1 cm. and the sum of their circumferences being less than, instead of (as is usual) much more than, the circumference of the stem of the pulmonary artery. There was a hemorrhage in the adventitia of the stem of the pulmonary artery extending along the left branch as far as the hilus of the lung.

Microscopic Postmortem Examination.—Microscopically the stem of the pulmonary artery showed slight sclerosis, the intima being 0.05 mm. thick. The media was thickened to 1.53 mm., and its elastic laminae were thicker and more closely set than usual. There was a great deal of well preserved extravasated blood in the adventitia.

The right and left arteries showed more marked sclerosis, the intima in places measuring 0.216 mm., but the changes were otherwise similar.

Of the intrapulmonary arteries more than 1 mm. in diameter, many were normal, but some showed marked patchy atheroma with intimal thickening, in places reaching 0.365 mm., or as much as 11 per cent of the external diameter of the vessel. The patches often had groups of fat-containing foam cells. The media and adventitia appeared normal. The most marked changes were present in the small muscular arteries, less than 1 mm in external diameter, seventy-nine of which were carefully measured. Nineteen (diameter, from 0.078 to 0.195 mm.;

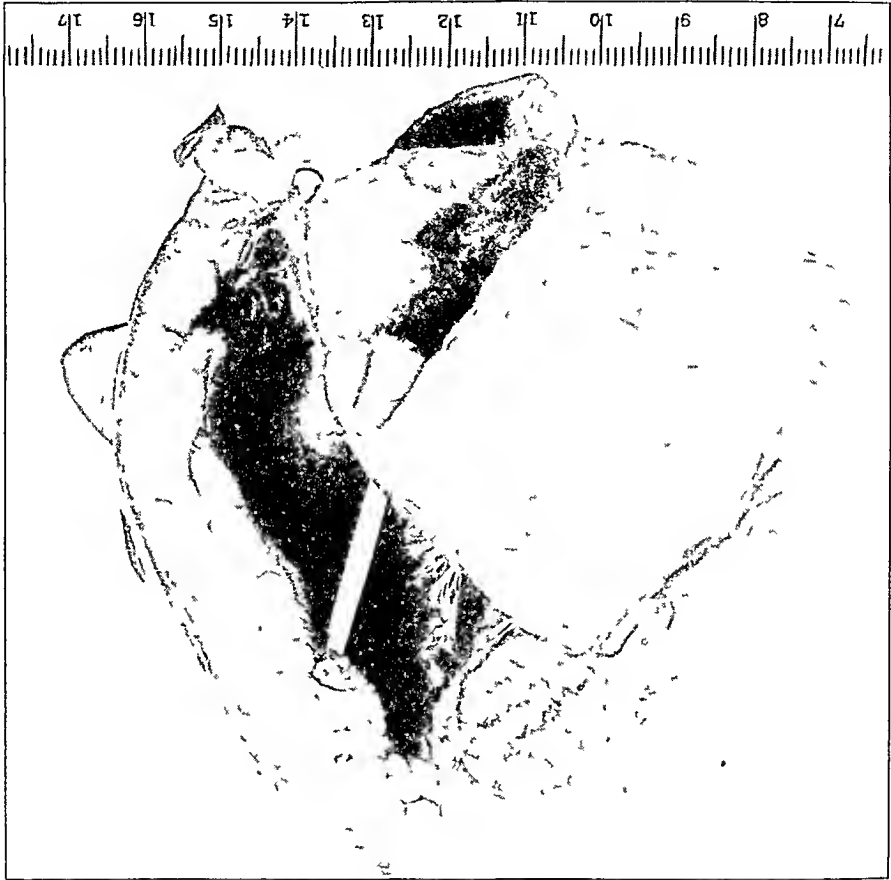


Fig. 21.—Gross appearance of the heart in case 1. The ventricles have been cut so as to show the hypertrophy of the right ventricle (on the left).

average, 0.123 mm.) of the 79 arteries were normal in all respects. Seven of the sixteen arteries less than 0.1 mm in external diameter were normal, and one other showed only hypertrophy of the media. Seven of the twenty-six arteries between 0.1 and 0.15 mm. in diameter were normal. Five of the twenty between 0.15 and 0.3 mm. in diameter were normal. No artery between 0.3 and 1 mm. in external diameter was entirely normal. Thus, most of the small arteries that were normal were among the smallest pulmonary arteries immediately before the arterioles. Apart from the nineteen normal arteries, six showed a normal intima. Eleven showed loose connective tissue intimal thickening, staining yellowish or pink with Van Gieson's stain and showing many round and spindle cells. This was often

accompanied by proliferation of the elastic tissue or of the intimal endothelium. This change was confined to the smaller muscular arteries, occurring in one of the nineteen arteries less than 0.1 mm. in diameter (5 per cent), in four of the twenty-six between 0.1 and 0.15 mm. (15 per cent) and in six of the twenty between 0.15 and 0.3 mm. (30 per cent).

In nine arteries endarteritis obliterans was present. In all, the intima was greatly thickened and the lumen was narrowed. In four the intima consisted of closely packed rounded or polygonal cells in a scanty fibrillar stroma. In five the intima consisted of loose fibrillar connective tissue with many round and spindle cells; this differed from the change in "fibrous intimal thickening" only

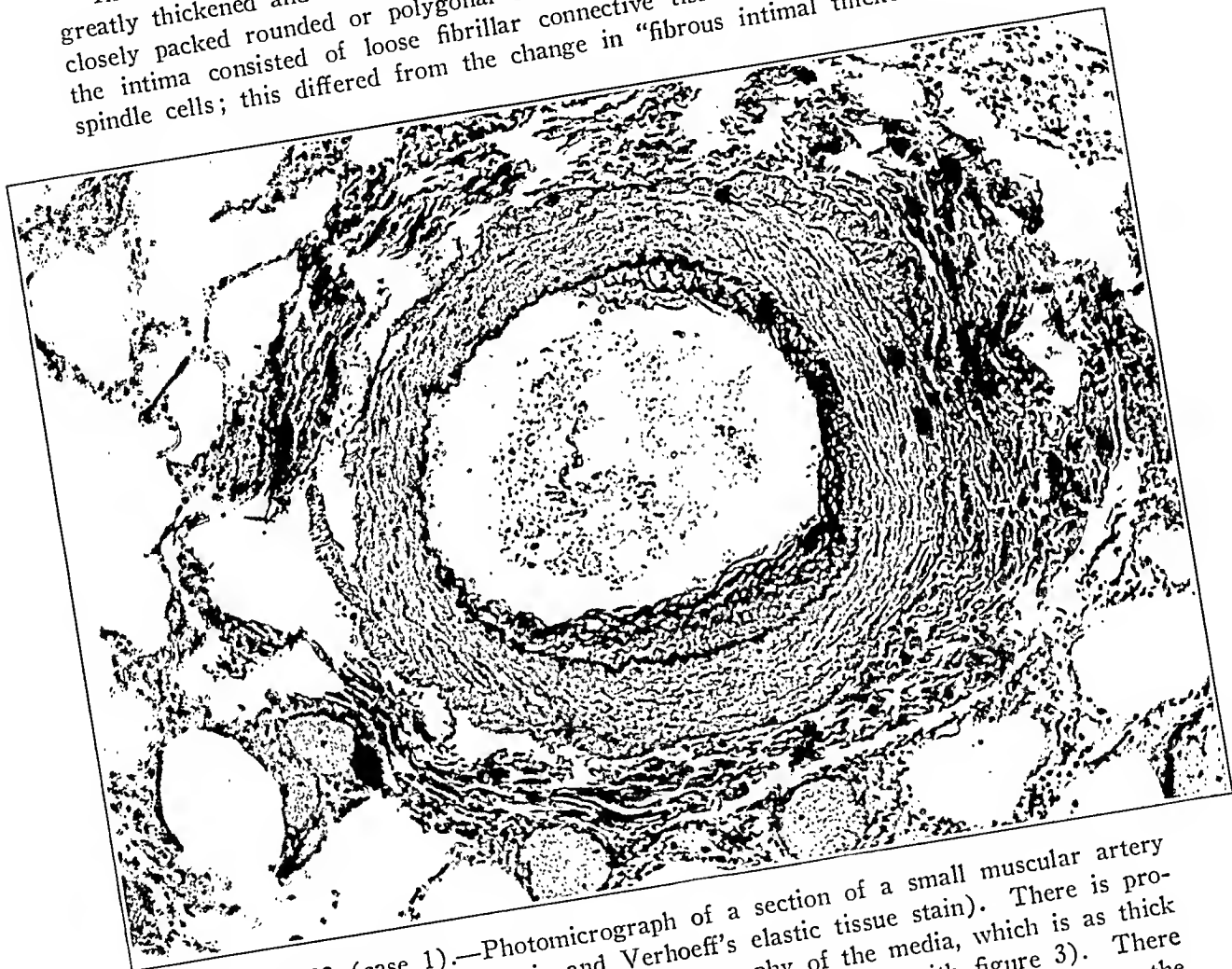


Fig. 22 (case 1).—Photomicrograph of a section of a small muscular artery ($\times 153$; Van Gieson's stain and Verhoeff's elastic tissue stain). There is proliferation of the elastica interna and hypertrophy of the media, which is as thick as that of a systemic artery of the same size (compare with figure 3). There is a layer of longitudinally directed muscle, cut transversely, external to the circular muscle.

in the greater thickness of the intima and the greater cellularity and looseness of the connective tissue. Usually no other changes were present in the affected vessels, which varied from 0.059 to 0.137 mm. (average, 0.105 mm.) in outside diameter. This change was present in seven of the sixteen arteries less than 0.1 mm. in diameter (44 per cent) and in two of the twenty-six between 0.1 and 0.15 mm. (8 per cent). No artery over 0.15 mm. in diameter was involved. Usually no other change was present in the affected vessels.

Proliferation of the elastica interna (fig. 22) was present in fifteen arteries. In some there was only splitting of the elastica interna over part of its extent; in others there was a thick layer containing five or six thick anastomosing elastic laminae with a little connective tissue and a few round and spindle cells. The change was often patchy and especially involved points where a side branch was arising. Other changes, especially hypertrophy of the media, also were often present. The vessels were from 0.109 to 0.498 mm. (average, 0.294 mm.) in external diameter. None was less than 0.1 mm. Three of the twenty-six between 0.1 and 0.15 mm. (12 per cent) in diameter, five of the twenty between 0.15 and 0.3 mm.

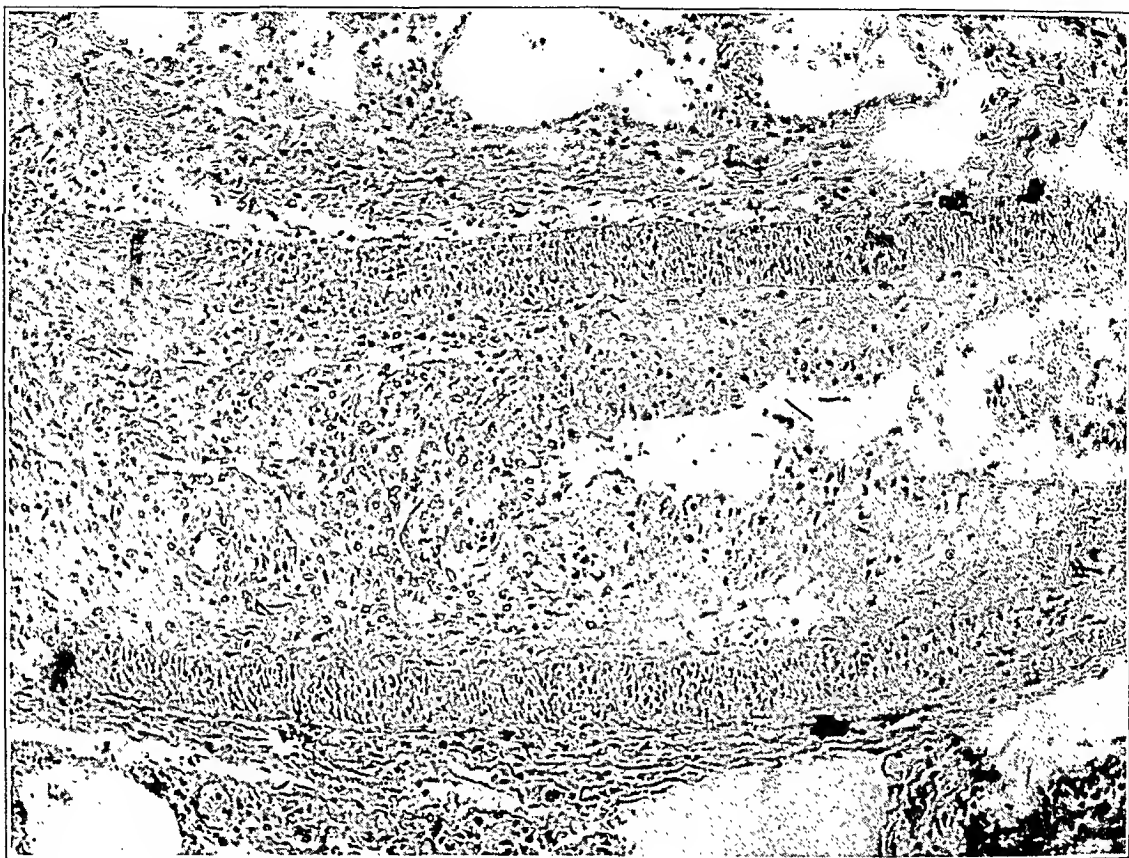


Fig. 23 (case 1).—Photomicrograph of a longitudinal section of a small muscular artery ($\times 160$; stained with hematoxylin and eosin). There is great proliferation of the intimal endothelium.

(25 per cent) and seven of the seventeen over 0.4 mm. (42 per cent) were involved. Thus, the larger of the small muscular arteries were especially affected.

Proliferation of the intimal endothelium occurred in twenty of the seventy-nine arteries measured and was the most striking change that was observed. A great proliferation of large, round or oval cells with clear vesicular nuclei greatly narrowed or obliterated the lumen (figs. 23 and 24). There was often also fibrous intimal thickening. The diameters of the affected arteries were from 0.109 to 0.266 mm. (average, 0.163 mm.). None of the arteries less than 0.1 mm. in diameter, ten of the twenty-six between 0.1 and 0.15 mm. (39 per cent) and ten of the twenty between 0.15 and 0.3 mm. (50 per cent) were involved. Eighteen of the twenty arteries with endothelial proliferation were between 0.11 and 0.21 mm. in

external diameter, and eighteen of the thirty-seven arteries of this size (50 per cent) were involved. The strictness with which the changes were confined to vessels of this size was remarkable (fig. 24). Often an artery of 0.4 mm. in diameter with hypertrophy of the media and proliferation of the elastic tissue gave rise to a branch with a diameter of from 0.16 to 0.18 mm., the lumen of which was almost blocked by endothelial proliferation. These might divide into branches with a diameter of from 0.07 to 0.1 mm., which were normal in all respects.

Hypertrophy of the media (fig. 22) was noted in thirty of the seventy-nine muscular arteries measured, the external diameter being from 0.06 to 0.913 mm.

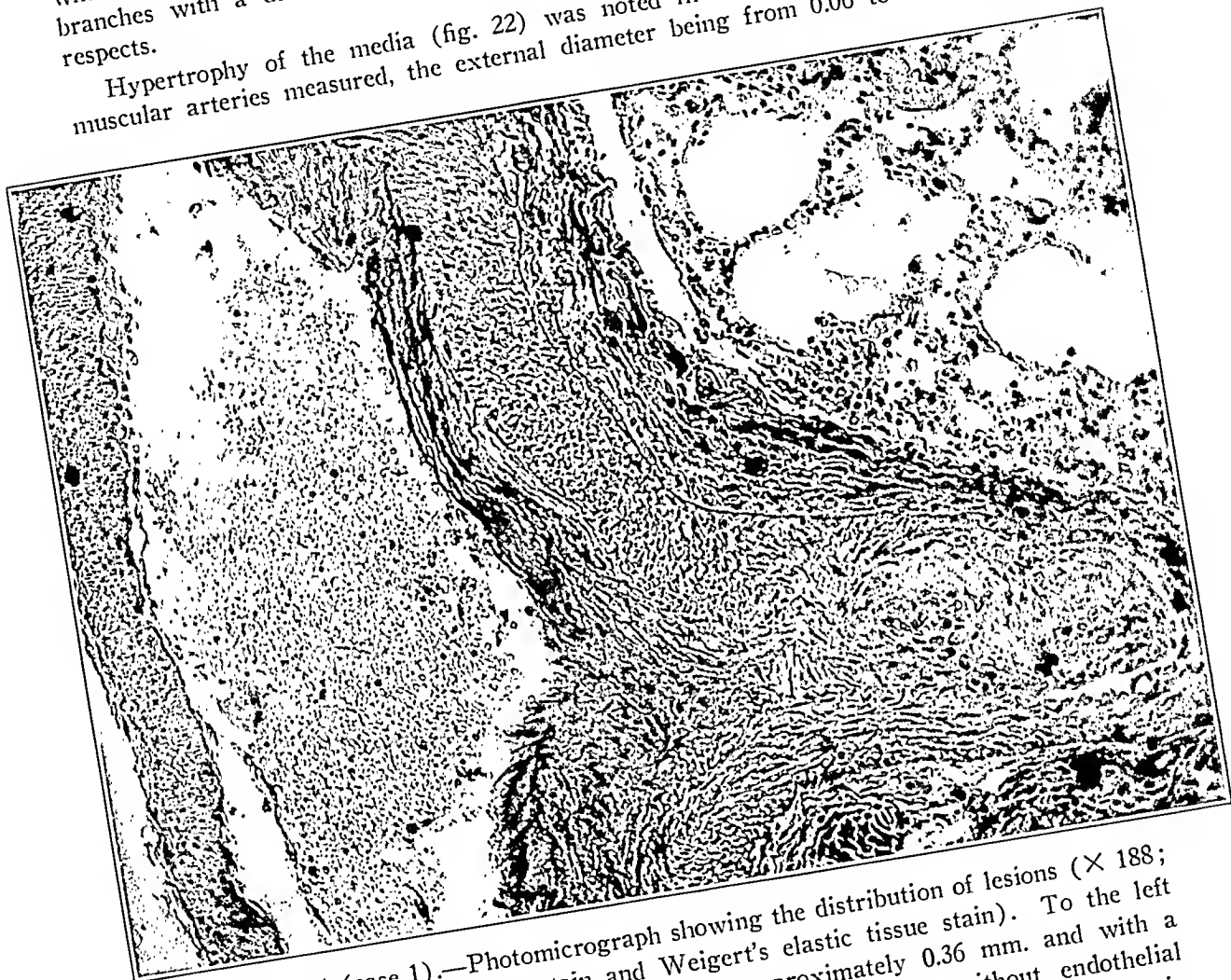


Fig. 24 (case 1).—Photomicrograph showing the distribution of lesions ($\times 188$; stained with Van Gieson's stain and Weigert's elastic tissue stain). To the left is an artery with an external diameter of approximately 0.36 mm. and with a hypertrophied media and proliferated elastica interna, but without endothelial proliferation. To the right is a branch of this artery approximately 0.17 mm. in external diameter, with a media of normal thickness and with the lumen almost obliterated by proliferated endothelium.

One of the sixteen arteries less than 0.1 mm. (6 per cent) in external diameter, four of the twenty-six between 0.1 and 0.15 mm. (15 per cent), eight of the twenty between 0.15 and 0.3 mm. (40 per cent) and all seventeen arteries over 0.3 mm. were involved. Thus, the larger of the small muscular arteries were chiefly involved. The media was heavy and muscular, resembling that of systemic vessels, and sometimes made up 30 per cent of the external diameter, its thickness being

equal to the diameter of the lumen. A little fine irregular elastic tissue was present among the muscle fibers. There was always a complete or incomplete layer of longitudinal muscle outside the normal circular muscle, and this sometimes made up a third of the total thickness of the media, sometimes being separated from the rest of the media by a fine elastic fiber. Sometimes there was also an incomplete layer of longitudinal muscle immediately beneath the internal elastic lamina.

The adventitia of many of the muscular arteries was thick and dense and showed foci of round cell infiltration. The arterioles and venules (fig. 22) were almost all normal, though a few showed slight endothelial proliferation. The small and large intrapulmonary and extrapulmonary pulmonary veins showed no abnormality. The aorta showed slight early atheroma. Some of the vasa vasorum of the stem of the pulmonary artery and some of the small bronchial arteries showed a thick layer of longitudinal muscle fibers outside the normal circular muscle of the media.

A branch of the coronary artery, 0.78 mm. in external diameter, showed a thickened media, the inner portion of which contained a great deal of homogeneous material which stained pink with Van Gieson's stain and pale blue with methylene blue and eosin, separating and distorting the muscle fibers. The adventitia was very thick and dense and contained a great deal of irregular elastic tissue and some longitudinal muscle. The appearance somewhat suggested that of a healed inflammatory lesion of the wall of the artery.

The heart showed a little perivascular fibrosis with a few lymphocytes and large mononuclears. No Aschoff bodies were seen.

CASE 2.—History and Course.—A woman, aged 27 at the time of her death in 1929, had been "mentally weak," and the history she gave was unreliable. She had never been strong. She had measles and mumps in childhood and influenza in 1918. In January 1923, fifteen months before her first admission, she had bronchitis with a cough and a great deal of sputum; she once spat up a little blood. Since then she had been dyspneic on exertion and was subject to cough with expectoration. There was an indefinite history of syphilis in her father.

At her first admission in April 1924 the temperature and the pulse and respiratory rates were normal. She looked well, and there was no cyanosis. There was a slight lumbodorsal scoliosis. The heart was somewhat enlarged, especially in the third left space, where the border of the cardiac dulness was 6 cm. from the midline. There was a pulmonary systolic murmur, and the pulmonary second sound was greatly accentuated. The spleen was palpable. The roentgenogram showed "a mediastinal shadow of unusual shape, increased in size in the region of the pulmonary artery, which had a definite pulsation." The electrocardiogram showed slight right axis deviation. The Wassermann reaction was negative on two occasions. The provisional diagnosis was congenital cardiac disease.

The patient was readmitted in January 1929 with an attack of bronchopneumonia of two days' duration, previous to which she had been well since leaving the hospital. The temperature ranged from 100 to 104.6 F., the pulse rate from 120 to 160 and the respiratory rate from 27 to 35. She was slightly cyanosed and extremely dyspneic. The left border of the cardiac dulness in the fifth space was 3 cm. outside the midclavicular line. There was marked dulness in the area of the pulmonary artery, with a slight continuous thrill, a short rough systolic and a longer blowing diastolic murmur there and to the right of the sternum. The pulmonary second sound was greatly accentuated. There were dulness and râles at the base of each lung. The liver was palpable. There was slight edema of the legs. The roentgenogram showed a greatly enlarged heart with marked promi-

nence in the region of the pulmonary arterial conus. The Wassermann reaction was negative. The clinical diagnosis was congenital cardiac disease with bronchopneumonia.

Gross Postmortem Examination.—Autopsy showed a fairly well nourished and well developed young woman with no edema. The liver was slightly smaller than usual and showed three or four depressed stellate scars. Otherwise the abdomen and its contents appeared normal. The right pleura showed slight, and the left extensive, adhesions. There was a thick purulent exudate in the trachea and bronchi, completely filling the small bronchi. The lungs showed many bronchopneumonic patches. Blood vessels were prominent on the cut surfaces. The pericardium contained 250 cc. of clear yellowish fluid. The heart was not weighed. It was greatly enlarged (15 cm. in transverse diameter). The right ventricle was dilated and markedly hypertrophied (11 mm. thick, compared with 13 mm. for the left ventricle). The left side of the heart appeared normal. The valves were normal, and there were no congenital defects. The aorta showed evidence of slight early atheroma. Its circumference was 5.5 cm. The pulmonary artery was greatly dilated (circumference, 13 cm.). The branches also were dilated. There was no constriction or obstruction. There were many small, scattered, raised, yellowish atheromatous patches in the stem and main branches. The pulmonary veins were not measured.

Microscopic Postmortem Examination.—Microscopically the stem of the pulmonary artery showed diffuse intimal thickening, with round and oval cells and clumps of fat-containing foam cells. In the depths of the intima there was a great deal of delicate elastic tissue and longitudinal muscle. The media and adventitia appeared normal. Many large intrapulmonary arteries showed similar changes. Others showed only slight intimal thickening, and others were normal. Many small muscular arteries were normal, but some showed fibrous intimal thickening, slight or marked, with narrowing of the lumen. The fibrous tissue was sometimes dense and hyaline and sometimes loose and cellular. In some the intima contained capillary lumens. A few arteries were blocked by dense fibrous tissue, with recanalization by small capillaries. The venules and small veins were greatly dilated and engorged. No large veins appeared in the sections. The lung tissue showed great congestion and acute bronchopneumonia. There were no chronic inflammatory or fibrotic lesions.

Comment.—Although deformities of the chest wall and pleural adhesions are both sometimes regarded as possible causes of secondary pulmonary vascular sclerosis, the changes in the second case were so slight that it seems unlikely that they had any influence.

It should be noted that the histologic changes in the two cases were different. In case 1 there was great endothelial proliferation and sometimes fibrous intimal thickening, with marked narrowing of the lumen. The hypertrophy of the media in the large muscular arteries and some atherosclerotic changes in the large elastic arteries were perhaps secondary to this. In case 2 the changes were those of ordinary atherosclerosis and were no greater than in many cases in which heart failure was not present and the right ventricle was of normal thickness. The review of the literature which follows shows that several different lesions have been reported under the name primary pulmonary vascular sclerosis.

INCIDENCE

Primary pulmonary vascular sclerosis is a rare condition. Moschowitz²¹² and Turnbull (quoted by Konstam¹⁵⁰) expressed a disbelief in its existence. MacCallum¹⁸⁷ found 1 case in 12,000 autopsies, and in that case slight emphysema was present. Reports of 66 cases have been found, in addition to the 2 previously described, but not more than 16, including case 1, described here, can be accepted without reserve. The others showed some factor, such as chronic cardiac or pulmonary disease, that was thought capable of causing secondary sclerosis either in severe form or, as in case 2, so mildly that it was improbable that it had any bearing on the condition. In others there was no autopsy or the description recorded was incomplete.

Sex.—Of the 68 patients, 36 were males and 32 were females.

Age.—The age varied from 6 weeks to 74 years, but most of the cases occurred in childhood, adolescence and early adult life.

MACROSCOPIC APPEARANCE

In order to justify a diagnosis of primary pulmonary vascular sclerosis all the factors commonly (though perhaps erroneously) thought to cause secondary pulmonary vascular sclerosis must be absent, and there must be marked hypertrophy of the right ventricle. Some authors have said that there should also be no systemic vascular sclerosis, though others have said that this is not necessary, and indeed the presence of a few fatty flecks in the intima of the systemic vessels is so common as scarcely to be considered pathologic. Finally, the changes in the pulmonary vessels must not be due to a specific infection, such as syphilis or rheumatism, though obviously inflammatory changes are not excluded as long as their origin is uncertain. The following 16 cases (some of them not well described) are the only ones that meet these requirements: case 1 described here, the cases of Tschistowitsch,³⁰⁰ Sanders,²⁶⁴ Bryant,⁵⁰ Ljungdahl,¹⁷⁶ Kuntschik,¹⁵³ and Schütte²⁷⁵; the 2 cases each of Goedel,¹¹⁷ Hart¹³¹ and Krutsch;¹⁵¹ and 1 case each of Eppinger's 5,⁹⁸ Mönckeberg's 2,²⁰⁸ Rössle's 2²⁵² and Ulrich's³⁰² 2 cases.

Heart.—The right side of the heart, especially the ventricle, was always enlarged and in many cases was said to be enormously hypertrophied and dilated. The right ventricle was from 5 to 14 mm. thick and sometimes, as in case 1, was thicker at the conus than at the apex. The left side of the heart was normal or atrophied and often looked like a mere appendage of the right, which usually formed the apex of the heart. An excess of pericardial fluid, never more than 200 cc., was present in several cases, including case 1. A great excess, such as Rogers²⁵⁴ noted in his cases in Indians (the descriptions of which are

not sufficiently detailed for them to be accepted without reserve as cases of primary sclerosis) and which he said was associated with great dilatation of the coronary sinus, was not noted in these cases.

Pulmonary Vascular System.—The main pulmonary veins were narrow in case 1, in Ljungdahl's case and in Krutsch's first case. The aorta was narrow in these same cases. Macroscopic changes in the pulmonary arteries were often slight, and in the cases of Eppinger, Schütte and Tschistowitsch they were absent. Moderate dilatation of the stem and main branches was present in case 1 and in 5 other cases. In many cases there were a few slightly raised whitish or yellowish patches or streaks in the intima of the stem and main branches, usually more marked in the branches of the second order and smaller and sometimes confined there. In Ljungdahl's case, which is unique, there was great thickening of the intima of the stem and main branches, with narrowing of the lumen. The changes, even microscopically, were less in the small branches. Thickening and rigidity of the smaller vessels, which projected open and gaping from the cut surface of the lung, were present in case 1 and in 7 other cases.

A partly organized thrombus occluded the right main pulmonary artery in Hart's first case. In Goedel's first case a large, fairly well organized thrombus partly occluded the stem of the pulmonary artery and spread to the right main branch and its branches, some of which were completely occluded. In Goedel's second case some medium-sized arteries were occluded by thrombi.

Lungs.—Pleural effusions were present in 3 cases (blood-stained in Schütte's cases). Eppinger said that the lungs, in contrast to the congestion of the other organs, were anemic and that the absence of clinical evidence of pulmonary congestion is an important point in the diagnosis of primary sclerosis. The lungs were anemic in 4 cases, including Eppinger's, but in 4 others they were markedly congested and edematous. In case 1 there was moderate congestion of the lower lobes. Thus, the fact that the obstruction to the pulmonary circulation lies on the arterial side of the capillaries does not always prevent the occurrence of pulmonary congestion.

A recent infarct of the lung was found in only 1 case.

Miscellaneous.—The organs other than the lungs usually showed chronic venous congestion. Great ascites was present in the cases of Ljungdahl and Schütte. The systemic vessels showed marked changes only in Bryant's case, though in case 1 and in some others there was a slight fatty change in the aortic intima.

MICROSCOPIC APPEARANCE

Microscopically several different lesions were described. In Ljungdahl's case there was enormous intimal thickening, reaching 1.44 mm. in

the stem and main branches of the pulmonary artery. The thickened intima consisted of loose connective tissue with round and oval cells and masses of fat. The small and medium-sized arteries were normal. This case is unique, though Ljungdahl himself later described a case in which there was a similar distribution of the lesions, which he then ascribed to organization of thrombi. In all the other cases the changes were much more marked in the small than in the large arteries, which in 7 cases, including case 1, showed only moderate atherosclerosis. In the other cases the large vessels either were normal or were not described.

In the small arteries there was fibrous intimal thickening, sometimes with few and sometimes with many cells. In the cases in which there were few cells there was usually a great deal of fine elastic tissue, and in the cases in which there were many cells and the change appeared to be inflammatory there was little or none. In all cases some of the vessels escaped, and in some (e.g., Schütte's) the changes were localized to only one part of the lungs. A few vessels were obliterated, and many were said to be greatly narrowed, though in some the pictures purporting to illustrate this showed what has been considered in the present investigation as only a moderate degree of sclerosis. In no other case were there the great endothelial proliferation, proliferation of the elastica interna and hypertrophy of the media shown in case 1. In a series of cases which are probably examples of primary sclerosis, though slight lesions of the lungs were also present, Bredt ⁴² found the chief lesion to be a peculiar fibrinoid necrosis of the media of the small vessels, with infiltration of red blood cells and sometimes aneurysmal dilatation. In some cases there was also reactive intimal thickening, though Bredt thought the lesion of the media was primary.

It is, therefore, obvious that primary sclerosis is not a pathologic entity but that several different conditions are included under the same name.

SYMPTOMS

The symptoms were chiefly those of failure of the right ventricle, for which no adequate cause can be found. Dyspnea was characteristically slight, and there was usually no orthopnea. This, in many cases, was in striking contrast to the severity of the cyanosis and edema. Cyanosis was usually intense, often deeper than any that is commonly seen except in cases of congenital cardiac disease, but in case 1 and in Ljungdahl's case, cyanosis was present only on exertion, and in 2 cases cyanosis was not mentioned. Polycythemia was often associated with the cyanosis, but sometimes it was not marked and, as in case 1, the red cell count was normal.

Edema was often even more prominent than cyanosis and was sometimes the leading symptom, being associated with ascites and pleural

effusions. In Ljungdahl's case (and also in Mattirole's,¹⁹⁵ in which the lungs were not normal, so that it is not included among the definite cases) ascites was the first symptom, and the clinical diagnosis was cirrhosis of the liver. In 6 cases, including case 1, edema was not present.

Palpitation was common, but was rarely troublesome.

Hypercyanotic angina occurred only in case 1, and there it was atypical in that there was no mention of an intensification of the cyanosis and that the pain radiated down the arms instead of deep into the chest.

Blood streaking of the sputum occurred in 1 case.

Nervous symptoms, such as somnolence, vertigo and syncope, sometimes developed, but were pronounced only in case 1, in which for 2 years there were attacks of syncope, with drowsiness and cyanosis, accompanied by muscular rigidity and incontinence and followed by vomiting.

Examination showed no physical signs of chronic pulmonary disease, though pleural effusions sometimes occurred as part of a general anasarca. Eppinger stressed the absence of evidence of congestion of the lungs, though in some of the cases reported there were crepitations at the bases.

The heart was usually slightly enlarged to the right or to the right and the left. The pulmonary second sound was usually greatly accentuated and in 3 cases, including case 1, it was followed by a soft diastolic murmur due to functional incompetence of the pulmonary artery. There was often a soft pulmonary and apical systolic murmur but no evidence of organic valvular disease. The pulse was usually small, regular and fairly rapid and the blood pressure was normal. The electrocardiogram, when mentioned, showed only right axis deviation, which in case 1 increased in degree over a period of two years. Roentgenograms showed a slightly enlarged heart with a prominent pulmonary artery and right ventricular conus, but with a normal left auricle in the oblique view. Eppinger stressed the absence of evidence of pulmonary congestion. Excessive pulsation of the hilar shadows was noted in some cases of functional pulmonary incompetence.

The duration of symptoms varied from five months to five years, the average being less than two years. The course was steadily downhill, and treatment was ineffective.

DIAGNOSIS

In typical cases it is possible to diagnose the condition. The chief points are: (1) severe cyanosis and edema, with comparatively little dyspnea (though as in case 1, cyanosis may be slight and edema absent); (2) clinical and electrocardiographic evidence of hypertrophy of the

right ventricle but not of the left; (3) an accentuated pulmonary second sound, perhaps with a pulmonary diastolic murmur, without murmurs indicative of valvular or congenital cardiac disease; (4) no clinical or roentgenographic evidence of chronic pulmonary disease; (5) roentgenographic evidence of enlargement of the right heart with prominence of the pulmonary artery and conus of the right ventricle, but with a normal shadow of the left auricle, and (6) no evidence of syphilis.

When mistakes have been made, the case was usually regarded as one of mitral stenosis or congenital cardiac disease, though occasionally the diagnosis of adherent pericardium with Pick's syndrome was made.

PATHOGENESIS

A. Nature of the Vascular Changes.—In some cases, both typical and with slight disease of the lungs, the change appeared to be inflammatory, with cellular connective tissue thickening of the intima and sometimes^r with scanty round cell infiltration of the media and adventitia. In others the primary change appeared to be due to hyaline degeneration of the walls of the small vessels ascribed to typhus infection¹⁵⁷ or a peculiar necrosis of the media⁴² due to some unknown toxin. In case 1 the cellular intimal thickening and the great endothelial proliferation (resembling that seen in a more localized form in cases of acute rheumatism) were probably due to the action of bacterial toxins, while the hypertrophy of the media and the hyperplasia of the elastic tissue in the somewhat larger arteries were probably secondary.

However, in most cases the changes appeared to be those of ordinary atherosclerosis and to be noninflammatory. Though it is agreed that in the systemic circulation hypertension is at the most a contributory factor in the development of atherosclerosis, most authors have suggested that primary sclerosis is caused by pulmonary vascular hypertension, due either to spasm of the pulmonary arterioles (which, since they consist merely of an endothelial tube surrounded by an elastic fibril with no muscle, is unlikely though not impossible) or to a congenital narrowness of the main pulmonary veins, such as has been described in a few cases, including case 1, in which case marked chronic venous congestion of the lungs would be expected. This is usually not the case. The narrowness of the pulmonary veins is probably an effect and not the cause of the diminished blood flow through the lungs. Some authors have suggested that an important factor is congenital inferiority of the pulmonary artery, which makes it unable to withstand the normal pulmonary arterial pressure. The resulting arterial lesions increase the blood pressure and so set up a vicious circle. There is no evidence to support this view.

(r) 109, 157.

Benda ²⁷ suggested that the condition may be identical with thromboangiitis obliterans, but the pathologic lesions are different. In cases in which thrombosis was a marked feature, such as those of Goedel, it was suggested that possibly a large embolus had broken up and become disseminated throughout the lungs, where it then organized.

Thus in a small group the cause is probably an unknown infection. In another small group possibly widespread embolism with organization is responsible. But in most, the cause is unknown.

B. Relationship of the Arterial Lesions to Hypertrophy of the Right Ventricle.—Most authors have assumed that the changes in the pulmonary arteries cause a marked rise in the pulmonary arterial pressure and hypertrophy of the right ventricle due to overwork. But doubts arise when the question is investigated closely. In all cases some vessels were normal. In some cases, such as case 2, the vascular changes were only moderate. Much more marked arteriosclerosis occurs without hypertrophy of the right ventricle. In some of the cases that have been reported the vascular changes were trivial. Ulrich ³⁰² described a case of primary sclerosis and another case in which almost identical symptoms and equally great hypertrophy of the right ventricle were noted at autopsy, with normal pulmonary vessels even on microscopic examination. It is generally agreed that in the systemic circulation the most extreme arteriosclerosis does not cause hypertension. According to reports in the literature,⁸ ligation of the pulmonary artery to one lung causes only a slight and transient rise of the pulmonary arterial pressure and a scarcely perceptible hypertrophy of the right ventricle even after many months. Multiple embolism of the smallest arterial branches in goats, to an extent causing death in a few hours,⁸⁷ causes only transient changes in the pressure in the right ventricle. This is because of the great reserve of small pulmonary vessels and their dissensibility. On the other hand, Schmidt ²⁷¹ has described a case of multiple embolization of the pulmonary vessels by tumor in which most of the small arteries were occluded by clumps of tumor cells with secondary thrombosis. The patient died of heart failure, and at autopsy hypertrophy of the right ventricle was manifest. It is impossible to deny that the hypertrophy and heart failure in this case were due to the obstruction of the pulmonary circulation, which, however, was more marked than in the cases of primary sclerosis that have been reported, as most of the small arteries were occluded and not merely narrowed. On the whole, therefore, it seems unlikely that the hypertrophy of the right ventricle and the heart failure are directly due to the lesions in the pulmonary vessels, since similar symptoms and hypertrophy of the right heart may occur without pulmonary vascular lesions, and lesions

(s) 81, 266, 268, 303.

greater than those in many of the cases that have been reported may occur without hypertrophy of the right ventricle or symptoms of heart failure. It should be remembered, as stressed by Lewis,¹⁷¹ that all the facts about ventricular hypertrophy are not yet known, and there is a great deal of evidence that it need not necessarily be due to overwork. It is possible that the pulmonary vascular lesions and the ventricular hypertrophy and failure are due to some unknown common cause rather than that they are related as cause and effect.

C. Symptoms.—The symptoms were those of failure of the right heart, with chronic venous congestion of the organs and edema. The slightness of the dyspnea was due to the absence of great congestion of the lungs, so that the vital capacity was not so diminished as in ordinary cases of heart failure. The cyanosis, which was a striking feature in many cases, is difficult to explain. Oxygenation of the blood occurs not in the small arteries, which are diseased, but in the capillaries, which are normal and through which the blood flow is if anything slower than normal, so that more time is given for gaseous exchange. No adequate explanation of the cyanosis has yet been offered. The hypercyanotic angina which occurred in some cases is also difficult to explain. It has been suggested that the pain was due to stretching of the sclerotic large pulmonary arteries by the rise in blood pressure during exertion. But the large arteries were often only slightly sclerotic or not at all, and the belief that ordinary angina is due to stretching of the aorta has practically been abandoned. It seems possible to reconcile hypercyanotic angina with the current theory that angina is due to myocardial anoxemia and so to make it a special type of ordinary angina. The cyanosis which was present in these cases was associated with imperfect oxygenation of the arterial blood and thus with a chronic myocardial anoxemia. During exercise the cyanosis, and therefore the myocardial anoxemia, increased, and the demand of the myocardium for oxygen increased. Pain therefore arose. It should be noted that in case 1, which was the only undoubted case of primary sclerosis in which cardiac pain occurred, there was a lesion of the coronary artery, with narrowing of the lumen, which no doubt diminished the supply of the impoverished blood to the myocardium.

Thus, the subject of primary pulmonary vascular sclerosis raises many problems of pathology and pathologic physiology which still await solution.

ENDARTERITIS OBLITERANS OF THE PULMONARY VESSELS

There is growing doubt as to the desirability of retaining the name endarteritis obliterans. By it is meant great thickening of inflammatory type of the intima of small arteries together with great narrowing or

obliteration of the lumen. The thickened intima consists of cellular connective tissue with lymphocytes and perhaps a few polymorphonuclears. There may be a few capillary lumens and some irregular elastic fibrils. A similar picture may result from the organization of thrombi or as a reaction to injury of the vessel wall or even physiologically as a result of disuse, as in the ductus arteriosus after birth or the uterine arteries after parturition. It is also difficult to distinguish it from ordinary arteriosclerosis of small arteries without lipoid deposition, since the intima may be cellular in degenerative and acellular in inflammatory cases.

In the pulmonary arteries endarteritis obliterans has been described in connection with chronic pneumonia, which was thought to be due possibly to rheumatism in a woman with mitral stenosis,¹³ in connection with anthracotic nodules in a patient who died of heart failure secondary to chronic pulmonary disease²²⁶ and in connection with what the authors thought (usually without adequate evidence) to be syphilitic disease of the pulmonary vessels.[†]

In the present series, changes in the small muscular arteries, which for the sake of convenience were called endarteritis obliterans, were present in 12 cases. There were two types of lesions. In the first there was pronounced and uniform connective tissue thickening of the intima with narrowing or even obliteration of the lumen. The connective tissue was sometimes dense but usually loose and cellular, with many fibroblasts and lymphocytes, some large mononuclears and in 2 cases a few polymorphonuclears. In 1 case a few multinucleated giant cells were present in the intima near foci of fibrocaseous tuberculosis, and in 2 cases there were a few capillary lumens. The 9 patients with this type of lesion were as follows: 1. A patient (case 1) with primary sclerosis, previously described. 2. A child of 13 months with a chronic pulmonary abscess. All the affected arteries were near the abscess. 3, 4 and 5. Three persons with chronic fibrocaseous tuberculosis. The affected arteries were all near tuberculous foci. 6. A woman with bronchiectasis. The affected vessels were all near dilated and inflamed bronchi. 7. A woman with hypertension. 8 and 9. Two men with emphysema and fibrosis of the lungs. In the last 3 cases no connection could be traced between the arterial changes and a local chronic inflammatory lesion, but in 1 case the changes seemed to be related to deposits of secondary growth in the perivascular lymphatic vessels. In no case was the change widespread enough to cause any material obstruction to the pulmonary circulation.

The second type of lesion (fig. 25) was found in 4 cases (in the case of primary sclerosis both types occurred). There was great

(†) 125, 231, 248.

intimal thickening, sometimes with obliteration of the lumen. The intima consisted of closely packed oval or polygonal cells with small central vesicular nuclei, separated from each other only by a delicate network of fine fibrils, which stained pink with Van Gieson's stain. At first glance such a vessel in transverse section looked like a nerve, the clear cytoplasm of the intimal cells with their well defined cell boundaries looking like the neurilemma and the space left after dissolving away the myelin sheath, while the nucleus looked like the axis cylinder. If a lumen was present at all, it was usually small and

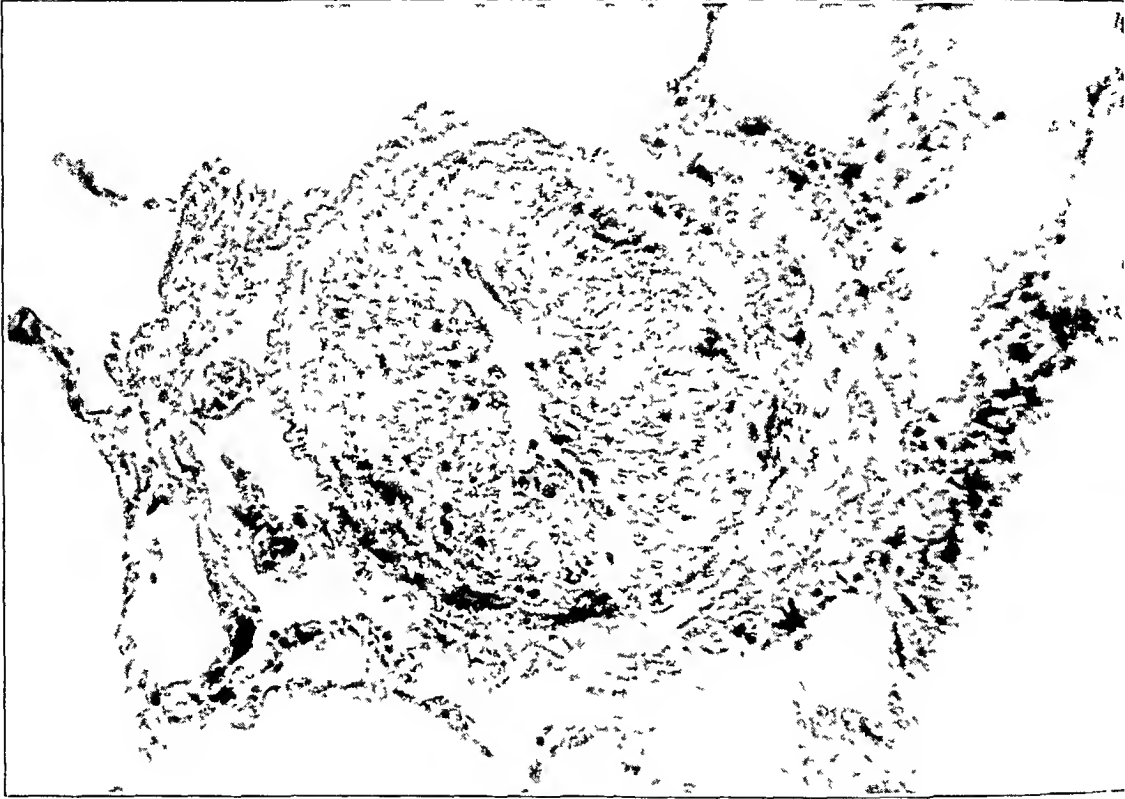


Fig. 25.—Photomicrograph of a section of a small muscular artery showing endarteritis obliterans ($\times 260$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). The greatly thickened intima consists of closely packed polygonal cells in a scanty fibrillar stroma. The lumen is considerably narrowed.

eccentric. Immediately beneath the endothelium was a fine, often fragmented elastic fibril. Sometimes there were one or more similar fibrils concentric to the lumen, between this and the internal elastic lamina, which was much thicker. In addition, a few irregular elastic fibrils were sometimes present in the intima. Only a few vessels in each case were affected. They often lay in thick strands of connective tissue, apparently representing interlobular septums, but occasionally they were noted in the parenchyma of the lung. Similar changes were more com-

monly seen in the bronchial arteries and the vasa vasorum of the pulmonary vessels. These changes were seen in the following patients: (1) A patient (case 1) with primary sclerosis; (2) a woman of 33 with chronic nephritis and hypertension; (3) a boy of 11 with rheumatic cardiac disease, and (4) a woman of 77 with coronary arterial disease and emphysema. There seemed to be no connection between this type of lesion and a local chronic inflammatory lesion, and too few vessels were involved to obstruct the pulmonary circulation seriously. The two types of lesion are thus distinct. The first type is probably a reaction to local irritation, especially an inflammatory irritation. The second is of obscure origin. Neither type is of any clinical importance.

HYPERPLASIA OF THE INTIMAL ELASTIC TISSUE

Hyperplasia of the elastic tissue of the intima is common in the systemic circulation, especially in the small renal arteries, where it is almost constant in some degree in elderly persons and is greatly increased in patients with hypertension. The elastica interna thickens and then splits into two parts, with a layer of connective tissue between. This may be repeated, so that five or six thick elastic laminae, more or less parallel to each other but sometimes anastomosing, may be formed, separated by a little connective tissue. The change occurs in the muscular arteries of the heart, brain, viscera and limbs and elsewhere but is always most advanced in the kidneys. The lesions are most marked in cases of hypertension, but the fact that they are always most advanced in the kidneys makes it unlikely that hypertension alone is the cause. Possibly the functional strain on the renal vessels resulting from the large volume of blood flowing through them makes them more susceptible to high blood pressure.

In the pulmonary circulation (figs. 22 and 26) elastic hyperplasia is much less common. Arrillaga⁹ said that it occurs in Ayerza's disease. Steinberg²⁸⁵ described it in the arterioles in 1 of his cases of primary sclerosis, and isolated cases have been described in cases of mitral stenosis.¹¹ In the present series, elastic hyperplasia was present in only 3 patients: (1) a man of 52 with hypertension and congestive heart failure, (2) a woman of 26 with mitral stenosis and congestive heart failure (fig. 26) and (3) a boy of 11 with primary sclerosis and congestive heart failure (fig. 22). Only the small muscular arteries were involved. In the first 2 cases only a few arteries were affected; in the last about 20 per cent of the small muscular arteries and 40 per cent of those over 0.3 mm. in diameter were involved. There were from three to six intimal elastic laminae, more or less parallel but anastomosing to some extent, each about as thick as the elastica interna. Sometimes the whole

(11) 43, 161, 306.

circumference of the artery was not involved, and the change was then most marked near the origin of the branches.

Congestive heart failure was present in all 3 cases, and the right ventricle was markedly hypertrophied (from 6 to 15 mm. in thickness) in all. It is therefore probable that pulmonary vascular hypertension was present, thus supporting the view that the change is a reaction to mechanical strain on the wall of the vessel due to hypertension.



Fig. 26—Photomicrograph of a section of a small muscular artery from a patient with mitral stenosis, showing elastic tissue hyperplasia ($\times 347$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). The elastica interna is split into from two to four layers with a little connective tissue between.

PROLIFERATION OF THE INTIMAL ENDOTHELIUM

Proliferation of the intimal endothelial tissue is rare apart from that which occurs in connection with organizing thrombi. Gordon¹¹⁸ described a case of subacute pulmonary arteritis in a case of congenital cardiac disease. The walls of the arterioles were infiltrated with round cells, and their lumens were filled with desquamated proliferated endothelium. In the present series endothelial proliferation was found in the following three patients aside from those in whom it was part of the organization of thrombi: 1. A woman of 34 with many pyemic abscesses in the lungs. Many of the arterioles, venules and small veins

near the abscesses were plugged by desquamated proliferated endothelial cells with one or more nuclei. Some showed phagocytosis of the red blood cells. The neighboring lymph glands also showed marked proliferation of the endothelium of their sinuses. 2. A woman of 26 with mitral stenosis and recent rheumatic endocarditis (see section on rheumatism of the pulmonary vessels). Several large elastic intrapulmonary arteries showed large masses of rounded or spindle-shaped endothelial cells projecting into the lumen. 3. A boy of 11 with primary pulmonary vascular sclerosis in whom about half of the smallest pulmonary arteries were involved. It is probable that in all three cases the change was related to infection. Only in the case of primary sclerosis were the changes widespread enough for the question of obstruction of the pulmonary circulation to be raised.

HYPERTROPHY OF THE MEDIA

The relationship of hypertrophy of the media to hypertension is unsettled, partly because of the difficulty of being sure how far post-mortem measurements correspond to the actual thickness of the media during life. Jores¹³⁸ said that the media may be either thicker or thinner than normal in cases of hypertension. Rössiter²⁵⁸ and others held that in diastole the muscle of the media actively contracts on the receding column of blood, thus helping to propel it ("the peripheral increases resulting in time in hypertrophy of the media. Eliaschewitz⁹⁴ described a case of mitral stenosis without hypertrophy of the right ventricle but with marked thickening of the media of the small pulmonary arteries. He believed that the contraction of the arteries was able to drive the blood through the narrow mitral orifice, thus making hypertrophy of the right ventricle unnecessary. But in this case practically all the muscle in the thickened small arteries was longitudinal, with only a thin outer layer of circular muscle corresponding to the normal media. It is difficult to see how longitudinal muscle could by its contraction narrow the arteries and so drive on the blood.

Hypertrophy of the media of the small pulmonary arteries is described in isolated cases of mitral stenosis,^v in a case of patent ductus arteriosus¹¹⁸ and in cases of chronic pulmonary disease.^w Campbell⁵¹ observed marked hypertrophy of the media of the small pulmonary arteries in cats kept for long periods under low oxygen pressures.

In the present series the media of the stem of the pulmonary artery, but not of the large intrapulmonary elastic arteries or of the small muscular arteries, was slightly thickened in cases of congestive heart

(v) 43, 306, 331.

(w) 221, 256, 331.

failure, in which the pulmonary vascular pressure might be expected to be high. But in the small muscular arteries in cases of congestive heart failure the average thickness of the media was 12 per cent of the external diameter, or a little less than the average normal thickness. Marked thickening of the media of the small arteries was noted in only 2 cases. One woman of 33 had chronic nephritis and hypertension and hypertrophy of the right ventricle (8 mm.) as well as hypertrophy of the left heart. A few arteries showed a thick media consisting of cir-

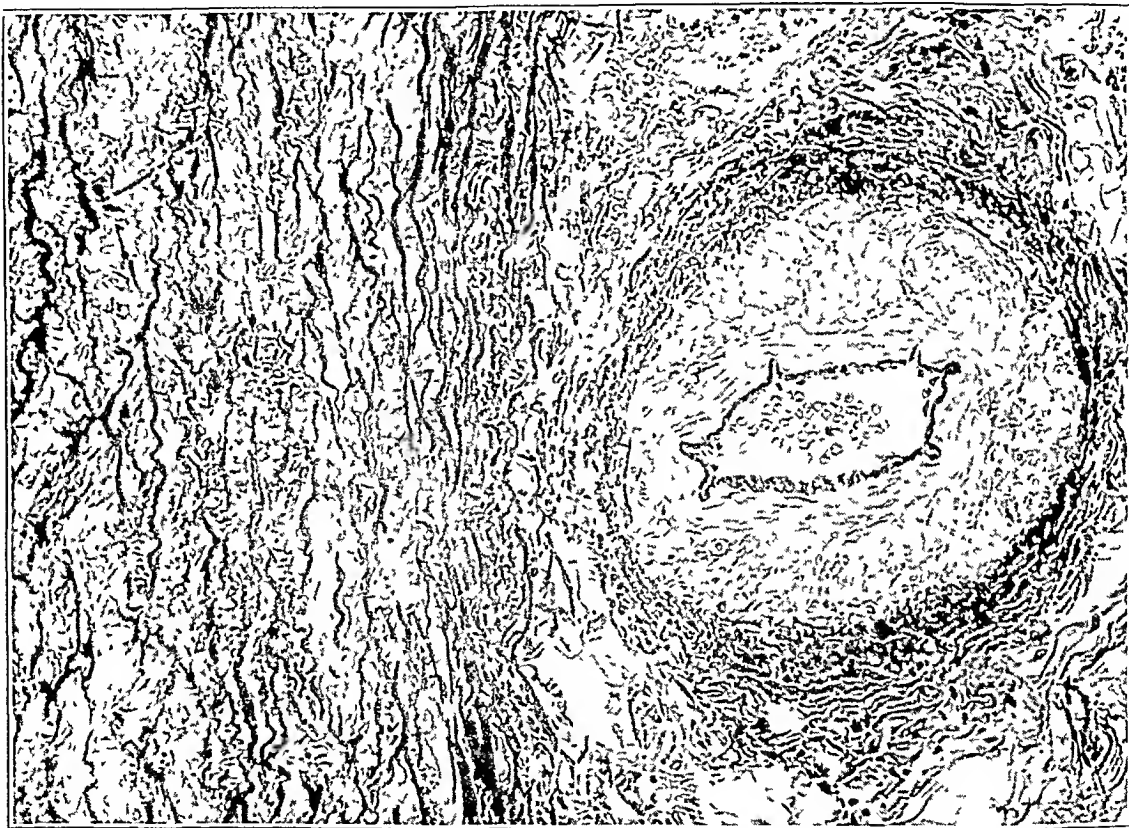


Fig. 27—Photomicrograph of a transverse section of the stem of a pulmonary artery ($\times 238$, stained with Van Gieson's stain and Verhoeff's elastic tissue stain). To the left is shown the outer part of the media and to the right, the inner part of the adventitia with a vas vasorum. Its media consists of a thin inner layer of circular muscle cut longitudinally and a much thicker outer layer of longitudinal muscle cut transversely.

cular muscle with a little fibrous tissue, but in most of the arteries the media was normal. In the patient (case 1) with primary sclerosis previously described (fig. 22), all the muscular arteries of more than 0.3 mm. in external diameter (i. e., those larger than the arteries showing endothelial hyperplasia) showed a thick muscular media, consisting chiefly of circular muscle but with a layer of longitudinal muscle outside this. It is possible that the hypertrophy of the media in this

case was due to the narrowing by endothelial hyperplasia of the smallest muscular arteries, though it is difficult to see why longitudinal muscle should also be present.

While hypertrophy of the media was rare in the pulmonary vessels, it was common in the vasa vasorum of the stem of the pulmonary artery (fig. 27) and to a less extent in the bronchial arteries and the vasa vasorum of the large intrapulmonary vessels. This change was usually in the vasa of the stem in 28 cases, in the bronchial arteries in 7 and in the vasa of the intrapulmonary vessels in 2. The intima was usually normal, though it sometimes showed any variety of disease. Outside of it was a layer of circular muscle, sometimes divided into four times the thickness of the circular muscle, sometimes the outer layer was separated from bundles by delicate strands of connective tissue. A few elastic fibrils were also present, and sometimes the outer layer was incomplete, typically of this change, the outer longitudinal layer was separated from the inner circular layer by a delicate elastic fibril. In the earliest stages forming in transverse section symmetrical triangular heaps of muscle cells cut transversely, with the base of the triangle applied to the circular muscle, at opposite poles of the cross-section of the artery. In 3 cases there was a great deal of fibrosis of the inner circular layer, which was replaced by dense connective tissue containing only the remnants of muscle, and in 1 case the external longitudinal layer was similarly fibrosed.

This change was present in the vasa and bronchial arteries in all the etiologic groups, in both sexes and at all ages, including the case of a child of 13 months. Usually only a few vessels in each case were involved. Jores¹³⁸ said that a little longitudinal muscle normally occurs in the adventitia, and that it is abnormal only when it is in great excess. Whether this statement has any bearing on the changes previously described, in which the outer layer of longitudinal muscle seemed to be part of the media, is difficult to say.

FIBROSIS OF THE MEDIA

Little has been written on the subject of fibrosis of the media, though Bell²⁶ said that in elderly patients replacement by fibrous tissue of atrophic muscle in the small muscular systemic arteries is common. In the small muscular pulmonary arteries the media normally contains no connective tissue, so that the presence of connective tissue, which stains pink with Van Gieson's stain, is abnormal. Fibrosis was present in 33 of the present series (31 per cent of the males and 36 per cent of the females). In 29 cases the change appeared to be degenerative. Patches of muscle were replaced by dense hyaline connective tissue (fig. 28). The change never involved the whole thickness or the

whole circumference of the media, though in several cases the medial fibrous tissue was continuous through gaps in the internal or external elastic membrane with that of the intima or adventitia.

The fibrosis seemed to be inflammatory in origin in 4 patients: 1. A man of 43 with syphilis of the aorta and pulmonary artery. The media of some of the larger muscular arteries was completely replaced over part of the circumference by dense fibrous tissue. The internal and external elastic laminae were both absent, and small vessels grew

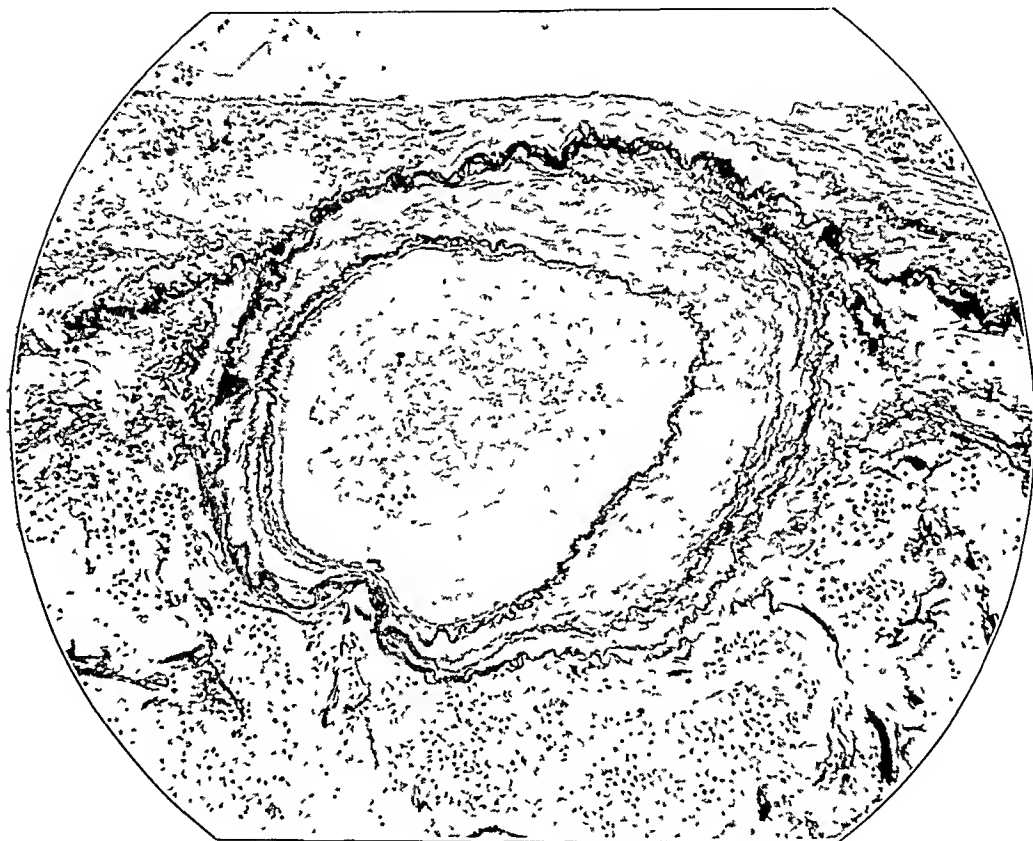


Fig 28—Photomicrograph of a transverse section of a small muscular artery ($\times 130$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). There is fibrosis of the media affecting the upper and right sides of the vessel.

into the thickened intima through the media from the adventitia (fig. 29). 2. A man with an aortic aneurysm compressing the left bronchus and with bronchiectasis of the left lung. In some of the small muscular arteries of the left lung the media in parts was replaced by vascular and cellular fibrous tissue. 3 and 4. Two cases of pulmonary tuberculosis. The media of some small arteries near tuberculous foci showed dense fibrosis of the media with round cell infiltration.

Fibrosis was present in 4 of 30 patients under 40 (13 per cent) and in 29 of 70 over 40 (42 per cent). Three of the 4 patients under

40 had rheumatic cardiac disease with congestive heart failure. In these the fibrosis may have been due either to healed rheumatic arteritis or possibly to the increased wear and tear due to the increased pulmonary vascular pressure. Of the patients over 40, 27 per cent in the "no cause" group and 90 per cent in the "pulmonary and cardiac disease" group showed fibrosis (table 31). Thus, fibrosis of the media, except in cases of inflammatory origin, is chiefly seen in elderly persons, but the presence of cardiac or pulmonary disease alone and especially together, increases

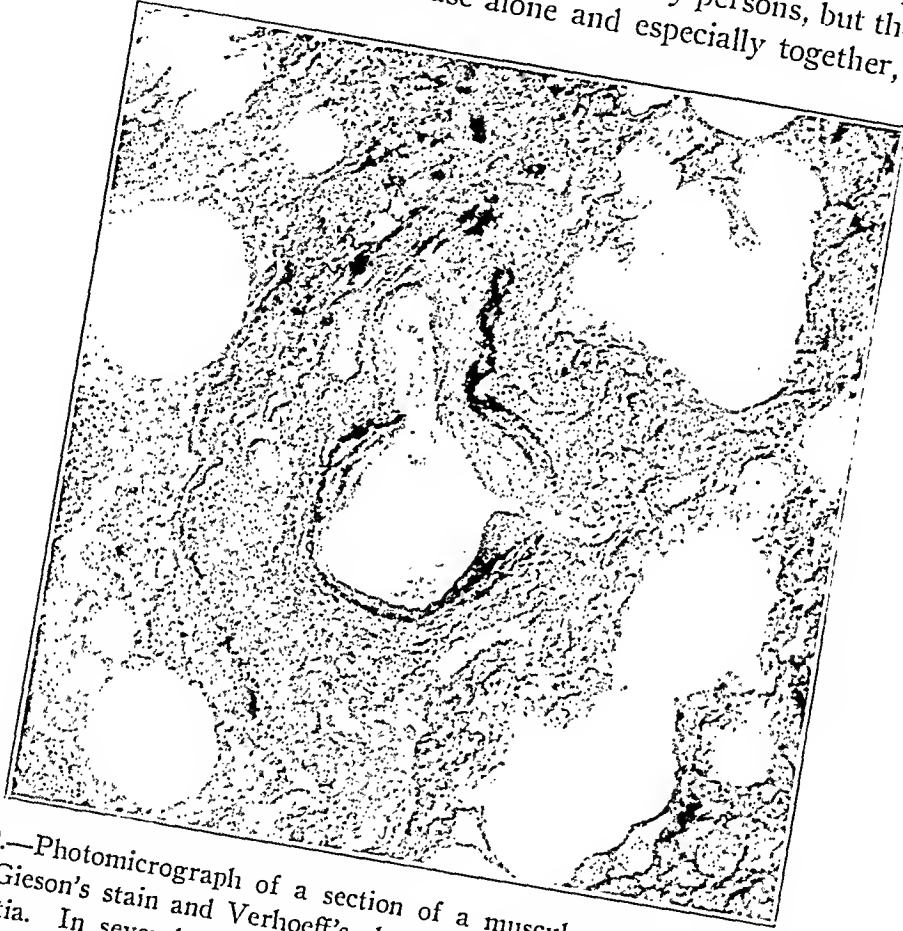


Fig. 29.—Photomicrograph of a section of a muscular artery ($\times 28$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). There is thick cellular adventitia. In several places the elastic tissue and muscle of the media have been destroyed (to the right at the origin of the branch, above and to the left) and cellular vascular connective tissue is continuous from the adventitia, through the destroyed media to the thickened intima.

the incidence, perhaps because of an associated rise in the pulmonary vascular pressure.

SYPHILIS OF THE PULMONARY ARTERIES

There has been an undue tendency, especially on the part of French and South American authors to exaggerate the frequency of syphilis of the pulmonary vessels and the importance of syphilis in the pathology of the vessels of the pulmonary circulation. Many cases have been

called syphilitic in the absence of satisfactory evidence and even in the presence of a satisfactory alternative cause. One case of syphilis of the pulmonary artery was found in the 100 cases in the present series. This will be described before passing on to a discussion of the condition.

REPORT OF CASE 3

History and Course.—G. T. L., a man, aged 43 at his death, gave a history of gonorrhea at the age of 17 and of syphilis at 19. Nine years before admission he began to have low substernal distress, especially when the stomach was empty. Two years later he had two severe hematemeses, followed by edema of the legs, ascites and dyspnea on exertion. The abdomen was tapped, and 9½ pints (4,500 cc.) of fluid was withdrawn. The liver was enlarged. The heart was large, and there were aortic systolic and diastolic murmurs. The blood pressure was 160 systolic and 110 diastolic. The Wassermann reaction was positive. The patient was markedly anemic.

TABLE 31.—*Distribution of Fibrosis of the Media According to Age and Etiologic Factor*

Etiologic Factor	Patients Less Than 40 Years of Age		Patients Over 40 Years of Age		
	Number of Pa- tients	Patients with Fibrosis	Number of Pa- tients	Patients with Fibrosis	
				Number	Percent- age
No cause.....	16	0	15	4	27
Pulmonary disease.....	6	0	23	11	48
Cardiac disease.....	2	2	5	2	40
Hypertension	3	1	6	1	17
Pulmonary and cardiac disease.....	3	1	10	9	90
Cardiac disease and hypertension.....	4	1	25
Pulmonary and cardiac disease and hypertension	3	0	..
Pulmonary disease and hypertension.....	5	3	60

After discharge ascites and edema persisted. Occasional attacks of nocturnal dyspnea began three years before admission to the hospital.

Examination showed that the patient was thin, the face was pale and the lips were brick red. The right side of the chest was fixed, and smaller than the left. There were many dilated veins across the upper part of the chest. The right side of the chest was dull on percussion, and faint bronchial breathing and many crepitations were noted. The base of the left lung was also dull. The left border of the cardiac dulness was 10 cm. from the midline, 2.5 cm. outside the midclavicular line. There were aortic systolic and faint diastolic murmurs. The peripheral vessels were thickened. Pulsus alternans was present. The abdomen was enormously swollen by ascites, and the skin was red and hot; the legs and thighs also were edematous and reddened.

The blood count showed 4,180,000 erythrocytes and 70 per cent of hemoglobin. The Wassermann reaction was positive. The electrocardiogram showed left bundle branch block and a low voltage.

Omentopexy was performed, and the patient died rather suddenly on the next day.

Gross Postmortem Observation.—Autopsy showed the body of a fairly well developed middle-aged man with great edema of the legs and scrotum and a

recent abdominal operative wound. The peritoneal surface was smooth and glistening. The right pleura was densely adherent to the lung except on its lower surface, where it was greatly thickened and formed a sac enclosing 1,300 cc. of serous fluid. The left pleura contained 900 cc. of fluid. The anterior portion of the lower border of the left upper lobe was bent on itself and adherent in its new position to less than half its normal size. The vessels and bronchi stood out prominently on the cut surface. The left lung was edematous and showed emphysema of the anterior border.

The pericardium contained 50 cc. of serous fluid and was densely adherent over the right auricle. There were more recent adhesions over the pulmonary artery and the base of the left ventricle.

The heart was moderately enlarged. The right ventricle was hypertrophied (from 5 to 9 mm. thick). The left ventricle was dilated and slightly hypertrophied (18 mm. thick at the base and 8 mm. near the apex). Near the apex the portion of the myocardium nearest the endocardium was scarred, and there was another scar at the base of the left ventricle. The aortic cusps showed a slender row of glistening granules at the lines of closure. The pulmonary cusps were slightly enlarged, and there was a small pinkish nodule in the center of each. The mitral and tricuspid rings were slightly dilated. The orifice of the right coronary artery was greatly, and that of the left slightly, narrowed. The left coronary artery showed a great deal of arteriosclerosis with calcification and narrowing of the lumen. The thoracic aorta showed marked atheroma and syphilitic aortitis, together with a tendency to bulging. The pulmonary arteries were dilated (circumference 8.4 cm. at the valve, 9.4 cm. 2 cm. above the valve and 8.7 cm. at the right hilus and 5.4 cm. at the left). The intima of the stem appeared normal. There were a few slightly raised whitish-yellow patches in the main right and left arteries, and in the middle lobe of the right lung was blocked at its mouth by a firm, adherent, reddish-gray thrombus. Just proximal to this there was an area about 1 cm. square of thickening and longitudinal wrinkling of the intima. The pulmonary veins appeared normal. The venae cavae and the portal, hepatic, splenic and superior mesenteric veins appeared normal.

The liver was normal in size. It was coarsely nodular and showed patchy capsular thickening. The spleen was large and firm, with patchy capsular thickening. The kidneys were small, the capsule was slightly adherent, the surface was coarsely granular with irregular scars and the markings were obscured.

Microscopic Postmortem Examination.—The pulmonary arterial stem showed slight patchy intimal thickening to a maximum of 0.07 mm. of the usual type. The media was greatly thickened (1.83 mm.). In the superficial part of the media were fairly large areas, in which muscle was absent, containing loose fibrillar connective tissue and elastic membranes together with some blood vessels, around some of which there was a scanty lymphocytic infiltration. The elastic tissue was not interrupted by this, only pushed aside. The adventitia showed a little diffuse lymphocytic infiltration. Many of the vasa vasorum showed a thick layer of longitudinal muscle outside an inner circular muscle layer, and in some the inner circular layer was replaced by dense fibrous tissue. The intima of the right main pulmonary artery was enormously thickened (from 0.42 to 1.59 mm.) with sudden diminutions and increases in the thickness, giving the impression of a series of parallel furrows in the intima. It consisted of dense connective tissue with a few round and spindle cells. Near the surface and parallel to it was a thin broken streak of calcification. In the depths of the intima were irregular clefts

left by the solution of cholesterol deposits. The media in most of its extent showed a normal structure, but in one long stretch its whole thickness was replaced by dense, rather vascular connective tissue with a few lymphocytes (fig. 30). The muscle and elastic laminae, except for a few fragments, were completely destroyed. There was slight diffuse lymphocytic infiltration in the adventitia, somewhat more marked around the vasa vasorum.

The branch to the right middle lobe contained a large unorganized, laminated thrombus of fused platelets and fibrin with very few red blood cells. The intima showed changes similar to those in the right main artery, but the media and adventitia were normal.

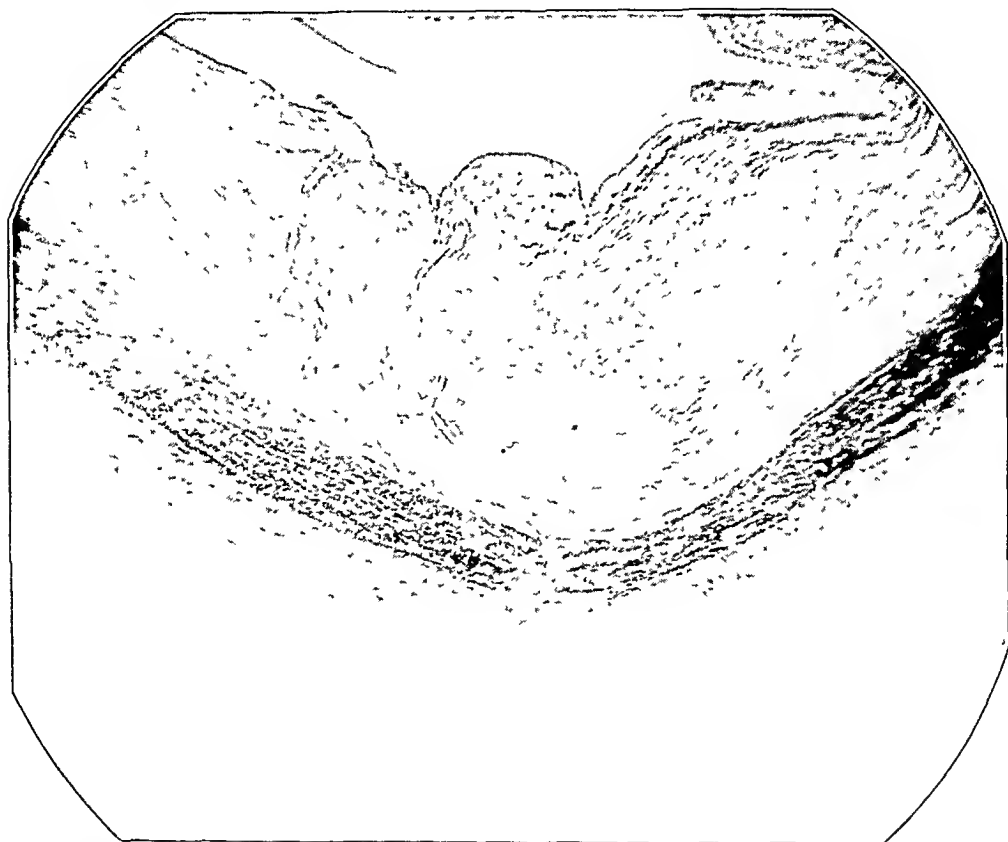


Fig. 30.—Photomicrograph of a section of a right main pulmonary artery ($\times 60$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). There is great intimal thickening, with numbers of fat spaces, and near the surface, to the right, a streak of calcification. The media near the center shows destruction of the elastic laminae and muscle and replacement by dense vasculocellular fibrous tissue. There is diffuse lymphocytic infiltration in the adventitia.

The elastic intrapulmonary branches (over 1 mm. in diameter) all showed patchy or diffuse intimal thickening, sometimes relatively enormous (e. g., 0.63 mm. in an artery 1.56 mm. in external diameter), often with great narrowing of the lumen. The intima consisted of connective tissue with numbers of lymphocytes, fibroblasts and irregular muscle cells and a great deal of elastic tissue in the depths. The media was normal. The adventitia often showed engorged capillaries and venules, and many of the vasa vasorum show narrowing of the lumen.

by great intimal thickening either by dense connective tissue or by closely packed oval or polygonal cells, similar to the second type of endarteritis obliterans, previously described.

One artery, 2.66 mm. in diameter, showed opposite the origin of a partly occluded large branch a conical horn-shaped mass projecting for 1.36 mm. into the lumen. It consisted of dense connective tissue with many elastic fibers, smooth muscle cells, lymphocytes and large mononuclears. There were also numbers of vascular lumens. The horn appeared to be due to the organization of a thrombus of the branch projecting into the parent vessel. This branch was a muscular artery, 0.96 mm. in diameter, the lumen of which was blocked for the first 1.5 mm. of its course by dense connective tissue containing elastic fibers, muscle cells and numbers of endothelium-lined lumens. Several other small muscular arteries showed similar changes, probably also due to the organization of thrombi. Others showed what appeared to be organized parietal thrombi, with many capillary lumens in the thickened intima. All the remaining small muscular arteries showed slight or great patchy or diffuse intimal thickening, often with great narrowing of the lumen. The thickened intima consisted of dense connective tissue, with round and spindle cells and often some irregular elastic tissue. The media in most of the arteries was normal, but in some (fig. 29) the muscle and internal and external elastic laminae were destroyed by the ingrowth from the adventitia into the thickened intima of dense or loose connective tissue, with lymphocytes, large mononuclears, capillary lumens and sometimes granules of coal pigment. This change occurred in some but not all the arteries with organized thrombi and in some others in which the intimal thickening was not obviously due to the organization of a thrombus. In these arteries the adventitia was thick and dense and showed diffuse infiltration with lymphocytes, plasma cells, large mononuclears and coal pigment.

The arterioles and venules showed thickened walls, often with a few lymphocytes and large mononuclears. The small veins showed a similar structure. The larger veins showed intimal thickening, sometimes with narrowing of the lumen, consisting of dense connective tissue with a few lymphocytes, large mononuclears and muscle cells. The media appeared normal except for a scanty lymphocytic infiltration in a few veins. The adventitia was thick and dense and showed a little diffuse lymphocytic infiltration.

The lung tissue showed a great deal of collapse, especially in the right lung, and thickening of most of the alveolar walls, with fibrosis and infiltration with lymphocytes and large mononuclears. The bronchi were dilated, and their epithelium was proliferated and desquamated, almost filling the lumen, together with lymphocytes and large mononuclears in some cases. The walls were swollen and infiltrated with lymphocytes, large mononuclears and a few plasma cells.

The aorta showed syphilitic aortitis with a great deal of scarring of the media. The descending branch of the left coronary artery was occluded by an organized thrombus.

Some of the arteries of the pancreas, kidney, spleen and adrenal glands showed connective tissue thickening of the intima and hyperplasia of the elastic tissue.

Comment.—The changes in the right pulmonary artery seemed to be undoubtedly syphilitic. They were similar to those in the aorta, which were characteristic of syphilitic aortitis. This, together with the positive Wassermann reaction, appeared to be conclusive evidence.

The changes in the small muscular arteries were more difficult to interpret. The changes in the intima (except those due to the organization of thrombi) were those of ordinary severe arteriosclerosis. The destruction of the media of some of the vessels and replacement by vascular cellular fibrous tissue might have been due to the following causes: 1. The growth of vascular connective tissue from the adventitia through the media into the intima may have been connected with the organization of thrombi, the vessels representing the organizing capillaries. This is unlikely because the change occurred in some vessels with no evidence of organizing thrombi and because in other cases the organization of thrombi was not associated with destruction of the underlying media by the ingrowth of vascular connective tissue from the adventitia. 2. The change may have been only the common senile fibrosis of the media, but in this condition the whole thickness of the media is rarely involved, and the fibrous tissue is dense, avascular and acellular. 3. The process may have been syphilitic. The lesions were similar to those in the aorta and right pulmonary artery, allowance being made for the different structure of the vessels. In systemic vessels of this size the common syphilitic lesion is endarteritis obliterans, though gummatous invasion followed by fibrosis may occur. It is therefore probable, though not absolutely certain, that the changes in the small arteries also were syphilitic. The other changes were non-specific.

The clinical features of the case were atypical. It was recognized that there was something unusual, but syphilis of the pulmonary vessels was not thought of, and even in the light of the postmortem observations it is difficult to see how the diagnosis could have been made. Indeed, it seems likely that the pulmonary vascular changes played comparatively little part in causing the symptoms.

COMMENT

There is an extensive literature on syphilis of the pulmonary arteries. Records of 65 patients thought to be syphilitic have been found in the literature, but in only 14 of these ^x could the diagnosis be taken as being reasonably well established. In the others autopsy was not performed or the postmortem observations were doubtful or definitely did not confirm the diagnosis of syphilis. In some cases rheumatic cardiac disease was present, and the changes in the pulmonary artery were most probably those of rheumatism and not of syphilis.^y

Of the 15 patients (including the 1 patient whose case is here reported), 7 were men, and 8, women. The age ranged from 28 to 60

.(x) 25, 57, 141, 154, 170, 231, 236 (2 cases), 238, 247, 311 (3 cases), 313.

(y) 53, 298, 317.

(average, 45). Thus, as far as can be judged from the scanty statistics available, syphilis of the pulmonary artery occurs rather earlier than that of the aorta, and there is not the same great preponderance of cases in men.

MORBID ANATOMY

Usually only the large vessels are involved, though in case 3 reported here and in Plenge's first case the small vessels showed changes which were possibly syphilitic, and in Peck's case they showed endarteritis obliterans. In the other cases in which the small vessels were examined, only nonspecific changes were observed. In none of the cases in which the diagnosis was reasonably well established were the changes confined to the small vessels though this was so in some of the cases in which the diagnosis was doubtful or obviously wrong.

It is rarely possible to make the diagnosis macroscopically, though in case 3 reported here and in some others^z there were suggestive scarring (linear, radiating or depressed) and localized bulging. In 7 cases aneurysms were present.^a In 3 of these^b the aneurysm involved the stem of the pulmonary artery and was fusiform. In another²⁵ there was a saccular aneurysm of the stem. In 1¹⁷⁰ there was a saccular aneurysm of the right pulmonary artery; in another, an aneurysm of the left pulmonary artery (Warthin,³¹¹ case 3), and in the last the exact site was not stated (Warthin, case 1). The saccular aneurysm usually contained a laminated thrombus. In Plenge's case 1 there was a dissecting aneurysm which had ruptured into the pericardium. Occasionally, recognizable gummas were present in the myocardium¹⁵⁴ or between the roots of the aorta and the pulmonary artery.³¹³

The stem and main branches of the pulmonary artery were usually dilated, but in Barth's case there was marked narrowing of the left pulmonary artery by a ring of fibrous tissue.

Secondary atherosclerotic changes in large and small arteries were common. Thrombi were present in the cases in which there were saccular aneurysms. In Ploeger's case the thrombus involved also the stem of the pulmonary artery, greatly narrowing it. Thrombi were also present in the cases of Karsner and Peck.

The heart was always slightly or greatly enlarged, its weight being from 430 to 750 Gm. In the cases of Ploeger, Plenge (case 1) and Warthin (case 2) only the right ventricle was hypertrophied; in the others both ventricles were involved. In Kux' case the cusps of the pulmonary valve were scarred and shrunken, and the tricuspid valve showed evidences of gummatous endocarditis. Syphilitic aortitis was

(z) 25, 236, 238, 313.

(a) 25, 170, 236, 238, 247, 311 (2 cases).

(b) 236, 238, 247.

present in all cases except those of Plenge (case 1), Peck and Letulle. Myocardial changes were present in some cases. In case 3 reported here there was the scar of an old infarct in the left ventricle. In Letulle's case there was a localized aneurysmal bulge of the right auricle. In Kux' case there were multiple myocardial gummas, and similar changes were present (though the diagnosis was not confirmed microscopically) in Handford's case.¹²⁴

The lungs often showed evidences of emphysema, fibrosis, bronchiectasis and old tuberculosis. Pleural adhesions were common. The other organs usually showed chronic venous congestion.

MICROSCOPIC CHANGES

Microscopic changes were commonest in the stem of the pulmonary artery and its main branches, where the appearances were those of syphilitic mäsarteritis and periarteritis. The intima usually showed slight or severe atherosclerosis, the greatest thickness in any case²³⁸ being 0.5 mm. It consisted of dense hyaline fibrous tissue, often with fat either lying free or in large foam cells. In Ploeger's case there was a deposit of lime near the surface. In his case, too, a partly organized thrombus was present, and there were capillaries in the depths of the intima even in areas not covered by the thrombus. In some cases^c the intima showed gummatous changes together with areas of necrosis and infiltration with lymphocytes and plasma cells. The media showed larger or smaller patches of fibrosis breaking up and destroying the elastic laminae. Often there was an ingrowth of vessels, frequently showing endarteritis obliterans, surrounded by an infiltration of lymphocytes, plasma cells, fibroblasts and occasionally³¹³ large multinuclear giant cells. In several cases^d gummas were present. The adventitia showed foci of infiltration with lymphocytes and often plasma cells, usually most marked around the vasa vasorum, which often showed endarteritis obliterans, sometimes so advanced as to occlude them completely.

The changes in the right and the left pulmonary artery ascribed to syphilis were similar to those in the stem. In Karsner's case the left artery was obliterated by dense fibrous tissue, apparently representing an organized thrombus.

Syphilitic changes have been described in the large intrapulmonary arteries in several cases, but in none of these was the diagnosis free from doubt, and usually it was clearly erroneous. The changes were usually those of simple atherosclerosis, though sometimes there was scanty round cell infiltration of the adventitia and media.

(c) 154, 231, 236 (case 2), 313.

(d) 57, 154, 311 (cases 1 and 2), 313.

In the small muscular arteries the changes were usually those of simple atherosclerosis, sometimes with thrombosis and organization. The case in which the lesions most clearly resembled those of syphilis was case 3 described here, in which many of the small arteries showed destruction of the muscle and elastic tissue of the media by cellular connective tissue.

Spirochetes were found only in Warthin's case. Arrillaga¹² reported the presence of spirochetes in the peribronchial and lymphoid tissue in one of his cases in which the lesion was almost certainly not syphilitic. The spirochete in this case was probably a saprophytic organism inhabiting infected bronchi, and not *Spirochaeta pallida*.

The lungs frequently showed emphysema, fibrosis and bronchiectasis, and those lesions probably were important in the production of the symptoms.

Syphilis of the pulmonary arteries is thus essentially a disease of the larger vessels, in spite of all that has been written on the importance of syphilitic pulmonary endarteritis obliterans in the production of symptoms (see the section on Ayerza's disease).

SYMPTOMS

The onset was usually insidious, with increasing dyspnea on exertion, but occasionally, as in Warthin's third case, in which the first symptom was profuse hemoptysis, it was sudden. In other cases the first symptom, often preceding others by years, was cough with expectoration and sometimes attacks of asthma. Dyspnea of some degree was absent only in Barth's case, in which there were no cardiac symptoms. Usually it was severe, with orthopnea, but in Letulle's case it was inconspicuous compared with the other symptoms. Cyanosis was common, being sometimes¹⁷⁰ the most striking sign. In others^e (including case 3 described here) it was absent. Edema was sometimes absent and usually was slight and appeared late, but in case 3 there were marked ascites, pleural effusion and edema of the legs. Blood streaking of the sputum or slight hemoptysis was common. In Warthin's case 3 there was severe and repeated hemoptysis that was not explained at autopsy. Retrosternal pain on exertion occurred in 3 cases^f (including case 3 described here), in all of which syphilitic aortitis was also present. Nervous symptoms were sometimes present. In the late stages of the disease some patients had troublesome insomnia, while others became increasingly drowsy and stuporous. Barth's patient had a stroke followed by progressive dementia twelve months before death. Attacks

(e) 25, 311, 313.

(f) 238, 313.

of Adams-Stokes' disease were present in 2 cases ^g in which there were gummas of the myocardium.

Examination often showed changes in the heart and lungs. In Ploeger's case of aneurysm of the pulmonary artery there was a localized bulge of the upper part of the precordia. The heart was usually slightly enlarged to the left. Enlargement to the right was rarely detected, perhaps owing to the frequent presence of emphysema. The pulmonary second sound was often accentuated. Pulmonary systolic murmurs were common, and a pulmonary diastolic murmur was heard in 3 cases (Clarke's and both of Plenge's), though it was difficult to distinguish it from the murmur of syphilitic aortic incompetence. Pericardial friction developed toward the end in Warthin's third case.

Signs of congestion and edema of the bases of the lungs and of chronic bronchitis and emphysema were common. In 2 cases ^h there was evidence of local pulmonary fibrosis. Clubbing of the fingers was present in 1 case.²³⁸

The liver was usually enlarged and in 1 case ²³⁸ the spleen also. Roentgenograms usually showed cardiac enlargement, particularly of the right side with a globular cardiac shadow. There was prominence of the left middle arc and in Ploeger's case evidence of enormous dilatation of the pulmonary artery, with no evidence of dilatation of the left auricle. The aorta also was often dilated.

The electrocardiogram in Kux' case showed complete heart block and right axis deviation; in Karsner's case, only an inverted T wave in lead III, and in the case reported previously, left bundle branch block and a low voltage.

The Wassermann reaction either was negative or was not mentioned in 7 cases,¹ in all of which the histologic lesions were characteristic of syphilis.

The course of the disease was almost always steadily downhill from the moment cardiac symptoms appeared though in a few cases there was transient improvement while the patient was in the hospital. The duration of symptoms in the cases in which it was recorded was from six weeks to forty years (average, eight years). In the cases in which there was a long history the symptoms for many years were merely those of chronic bronchitis, and it does not seem legitimate to attribute those symptoms to syphilis of the pulmonary arteries, though some authors have done so. Symptoms of heart failure usually did not last for more than a few months, though occasionally mild heart failure lasted for years. The usual mode of death was progressive congestive

(g) 124, 154.

(h) 25, 238.

(i) 25, 170, 231, 236, 238, 311, 313.

heart failure, with increasing dyspnea, cyanosis and edema. In some cases death was sudden, owing to thrombosis of a large pulmonary artery¹⁷⁰ or to rupture of a dissecting aneurysm of the pulmonary artery into the pericardium,²³⁶ in an attack of Adams-Stokes' disease¹⁵⁴ or in an attack of angina.³¹³

DIAGNOSIS

Diagnosis is difficult and often impossible in the present state of knowledge. Syphilis of the pulmonary arteries may be suspected if in a syphilitic patient there is heart failure with or without marked cyanosis and with evidence of hypertrophy of the right ventricle on physical examination (enlargement of the heart to the right, forcible right ventricular pulsation in the epigastrium, accentuated pulmonary second sound), by roentgenograms (enlargement of the right ventricle, prominence of the conus of the right ventricle and of the pulmonary artery) and by electrocardiogram (preponderance of the right ventricle). Roentgenographic evidence of an aneurysm of the pulmonary artery, in the absence of congenital cardiac disease, is also important. In most of the cases that have been reported these requirements were not fulfilled.

TREATMENT

Treatment in the stage of congestive heart failure is hopeless. Probably efficient treatment of early syphilis would prevent the occurrence of heart failure. If a diagnosis could be made before heart failure occurs, perhaps antisiphilitic treatment could hold the condition in check for years. When congestive heart failure is present, only symptomatic treatment with rest, digitalis and diuretics is possible. This can only delay, not prevent, the fatal issue.

AYERZA'S DISEASE

The concept of Ayerza's disease has dominated the American, English and French literature for thirty years. The meaning of the term is not fixed. To some it means any condition of cardiac failure associated with disease of the pulmonary vessels. Others identify it, unjustifiably, with primary pulmonary vascular sclerosis. Ayerza, of Buenos Aires, in 1901 described in an unpublished clinical lecture a case of heart failure with such marked cyanosis that the patient was almost black (*cardiaco negro*). At autopsy there were dilatation of the bronchi, peribronchitis, and hypertrophy and dilatation of the right auricle and ventricle. The pulmonary vessels were not mentioned. In 1905 Escudero found at autopsy in a similar case evidence of atherosclerosis of the stem and main extrapulmonary and intrapulmonary branches of the pulmonary artery. Marty in 1909 first called the condition Ayerza's disease. In 1912 Arrillaga concluded that the arterial

lesions were secondary to chronic bronchopulmonary disease. In 1913 he⁸ stated that the chief cause of the symptoms was chronic respiratory disease with emphysema and that chronic infections, such as syphilis and malaria, and chronic alcoholism sensitize the vascular system so that mechanical changes in the pulmonary circulation, which usually produce only slight changes in the pulmonary vessels, cause marked lesions. In 1916 he described a case in which there was an aneurysm of the pulmonary artery. In 1917 Barlaro²² said that the condition might be due to many causes, of which syphilis was the commonest. In 1917 Warthin³¹¹ described a case of syphilis of the pulmonary artery in which *Spirochaeta pallida* was demonstrated in the lesions. This patient was pale and showed none of the symptoms of Ayerza's disease, but since then the Argentinian authors have been strongly biased in favor of a syphilitic origin of Ayerza's disease. In 1921 Arrillaga¹² described a case with pulmonary lesions which were termed syphilitic bronchitis and bronchopneumonia in which he found a spirochete which he assumed to be *Spirochaeta pallida* in the bronchial lesions and in the adventitia of the arteries. The description was inadequate, and it seems probable that it was really a nonspecific spirochete of the kind so often found in the mouth and in infected bronchi. By 1924 Arrillaga⁹ had come to the conclusion that the essential factor is syphilis of the pulmonary arteries, and that chronic pulmonary disease, mitral stenosis and other conditions are important only in that by putting a strain on the pulmonary arteries they favor the localization of the syphilitic process there. But the evidence of the syphilitic nature of the pulmonary arterial disease in Arrillaga's cases is more than doubtful, and some Argentinian authors, for instance, Brachetto-Brian,⁴⁰ have stated that the lesions in each of their cases was merely atherosclerosis. In 1926 Escudero,¹⁰⁰ another of Ayerza's pupils, said that all patients with chronic pulmonary disease who die of failure of the right heart are deeply cyanosed and are therefore *cardiaques noirs*, but that in the absence of the lesions that he believed characteristic they do not have Ayerza's disease; conversely, patients with Ayerza's disease in the early stages are not cyanosed, and therefore are not *cardiaques noirs*. The lesions that he believed to be necessary for the diagnosis of Ayerza's disease are bronchial syphilis and obliterating sclerosis of the pulmonary vessels, which need not be syphilitic. Brachetto-Brian⁴⁰ expressed the belief that there are no specific lesions of Ayerza's disease. There is chronic disease of the bronchi and lungs, which may be, but usually is not, syphilitic; there is disease of the pulmonary vessels, usually atherosclerotic, but occasionally syphilitic, and there is hypertrophy with ultimate failure of the right heart. Syphilis, he said, is often present even when the lesions in the lungs and arteries are not syphilitic, so that a syphilitic soil favors the development of the disease. He regarded

the pulmonary lesions as primary, the vascular lesions being of the nature of a hypertrophic process followed by degeneration. The pulmonary arterial lesions in themselves he considered to be of little importance.

It is thus clear that there is no general agreement as to what constitutes Ayerza's disease. The consideration of some of the cases which have been described, now to be undertaken, raises the question as to whether the retention of the name is justified. Reports of 20 cases have been collected from the literature. Fifteen of the patients were men, and 5, women. The ages ranged from 28 to 62 years (average, 53).

MACROSCOPIC CHANGES

The heart was always enlarged, and the right auricle and ventricle were hypertrophied and dilated, the thickness of the ventricle ranging from 5 to 20 mm. The left auricle and ventricle were occasionally atrophic,^j but more usually they were hypertrophied, though not so much as the right. In several there was marked sclerosis of the coronary artery. In 1 case³³⁴ the cusps of the pulmonary valves were slightly thickened, but competent; in another⁵³ there was mitral stenosis, though the atheroma of the pulmonary arteries was ascribed, without a vestige of evidence, to syphilis. The aorta was occasionally narrow and hypoplastic.^k Sometimes it showed syphilitic aortitis.^l

The stem and main extrapulmonary and intrapulmonary branches of the pulmonary arteries were occasionally normal,⁵³ but usually there was atherosclerosis, most marked in the large intrapulmonary branches, diminishing in the extrapulmonary branches and often absent in the stem. In the smaller branches the patches at times somewhat narrowed the lumen, but the larger branches were, if anything, dilated. The smaller branches often were thick-walled and gaped widely on the cut surface of the lung. Thrombi were sometimes present^m in small or large branches. In Ploeger's case²³⁸ syphilis of the pulmonary artery with aneurysmal dilatation was present. In 3 of Arrillaga's cases¹⁰ "aneurysmal" dilatation was present, and in 1 case the aneurysm had burst into the pericardium, but in none was there convincing evidence of syphilis.

Dense local or general pleural adhesions, chronic bronchitis with moderate tubular dilatation of the small and medium-sized bronchi, sometimes localized saccular bronchiectasis,ⁿ marked emphysema and

(j) 150, 238.

(k) 47, 150.

(l) 47, 54, 238, 334.

(m) 9, 40, 54, 238.

(n) 12, 40, 47, 238.

peribronchial and perivascular fibrosis, or occasionally atelectatic fibrosis of one or more lobes,^o were present in practically all cases. In some cases⁴⁸ there were partially healed gummas destroying small bronchi and blood vessels. In all cases the lungs were congested and edematous, but infarcts were unusual even in the cases of arterial thrombosis.

MICROSCOPIC CHANGES

Microscopically the stem of the pulmonary artery sometimes showed more or less marked atherosclerosis,^p and in 1 case there was a partly organized thrombus.²³⁸ The media was usually normal but in 1 case it showed syphilitic mesarteritis,²³⁸ in 1 a broad band of dense fibrous tissue⁴⁷ and in 1 slight round cell infiltration,³³⁴ changes that were possibly syphilitic. The adventitia occasionally^q showed round cell infiltration, chiefly perivascular and sometimes consisting predominantly of plasma cells. In the large extrapulmonary and intrapulmonary pulmonary arteries atherosclerosis was usually present, and thrombi, often organized, were seen. The media was usually normal apart from minor changes in the amount of elastic tissue though occasionally it was sclerosed¹⁶⁷ and in 1 case³³⁴ there was a little round cell infiltration. The adventitia occasionally was thickened and sometimes showed slight round cell infiltration.

The small arteries were often narrowed, though sometimes they were dilated.^r The intima was thickened in many, sometimes to the point of obliteration, by dense fibrous tissue or sometimes by organized thrombi.⁴⁰ The media was normal except in 1 case,³³⁴ in which it showed slight round cell infiltration. The adventitia occasionally showed foci of lymphocytes and plasma cells,^s described as miliary gummas.

SYMPTOMS

The onset was usually insidious. It was often preceded for many years by chronic cough with expectoration, but sometimes the earliest symptoms were those of gradually increasing congestive heart failure. Escudero¹⁰⁰ divided the course of the disease into three stages: 1. A prolonged bronchitic stage differentiated from ordinary chronic bronchitis only by the presence of polycythemia. The physical signs of chronic bronchitis and emphysema and sometimes of localized fibrosis of the lungs^t are present. Sometimes this stage is absent, though often,

(o) 47, 238.

(p) 40, 47, 150, 334.

(q) 47, 238, 334.

(r) 12, 334.

(s) 2, 12.

(t) 47, 331.

even when the first symptoms are those of heart failure, the physical signs of chronic bronchopulmonary disease are present. 2. A stage of compensated cardiac disease, in which in addition to the foregoing, the physical signs of enlargement of the right heart are present. It is unusual for the patient to come under observation at this stage, and the signs of enlargement of the right heart are notoriously difficult to detect. 3. The stage of heart failure, with increasing dyspnea on exertion, which, however, is often slight compared with the other symptoms, great edema with ascites (this also is sometimes not marked) and deep cyanosis, often associated with headache, mental confusion and somnolence. In the cases reported the heart was usually slightly or moderately enlarged, especially to the right. Its rhythm was rapid and regular (in 1 exceptional case ⁵⁴ there was auricular fibrillation). Gallop rhythm, best heard over the right ventricle, was sometimes present.^u There were often systolic murmurs at the mitral, tricuspid and pulmonary areas and occasionally ⁹ a diastolic murmur of relative pulmonary incompetence. The pulmonary second sound was often but not always accentuated.⁵⁴ The red blood cell count ranged from 5,280,000 to 8,500,000. The leukocyte count also was sometimes raised, the highest recorded being 20,500. The roentgenogram usually showed moderate enlargement of the heart to the right and dilatation of the pulmonary artery but not of the left auricle. The electrocardiogram, in the few cases in which it was recorded, showed preponderance of the right ventricle, sometimes with inversion of the T wave in leads II and III.^v In 1 case ⁹ there was bundle branch block of the common type. The Wassermann reaction was positive in 11 cases, negative in 3 and not recorded in 6.

The course of the disease after heart failure has appeared was usually steadily progressive, but occasionally remissions lasting for a few weeks or months occurred.^w Death usually was due to heart failure, though sometimes it was due to some intercurrent disease, especially bronchopneumonia. The duration of cardiac symptoms was usually from one to four years, but the bronchitic symptoms may have been present for many years before heart failure occurred.

COMMENT

It is clear that there is nothing specific about the symptoms, which are those ordinarily recognized to be due to heart failure secondary to chronic bronchopulmonary disease. In such cases hypertrophy of the right ventricle is known to occur, though probably it is not so common as

(u) 2, 9, 167.

(v) 47, 150.

(w) 16, 47, 238.

is usually believed. Independent cardiac disease is usually present, in addition to the chronic pulmonary disease, and it is noteworthy that in the cases of Ayerza's disease that have been recorded the left as well as the right ventricle was often found to be hypertrophied, and coronary arterial disease and syphilitic aortitis were also commonly present at autopsy. Cyanosis is always marked when heart failure is complicated by severe chronic bronchopulmonary disease, and polycythemia usually accompanies chronic cyanosis of whatever cause. The lesions in the pulmonary arteries almost always seem to be those of atherosclerosis of a degree less marked than that in some cases in which there are no cardiovascular symptoms. True syphilis of the pulmonary arteries rarely occurs with this syndrome, and it sometimes occurs without the symptom complex of Ayerza's disease. Syphilis was proved to be present in only half of the cases that have been reported, and in only 1 of these was there acceptable evidence that the pulmonary arterial lesions were due to syphilis.

There is thus no clearcut, universally acceptable definition of Ayerza's disease, the term having a different significance to almost every writer on the subject; the lesions in the cases that have been reported were merely those of chronic pulmonary disease with moderate atherosclerosis of the pulmonary vessels and hypertrophy of the right ventricle; and the symptoms were merely those of heart failure associated with chronic disease of the lung. There seems to be no good reason for retaining the term Ayerza's disease.

(To be concluded)

Progress in Internal Medicine

SYPHILIS

A REVIEW OF THE RECENT LITERATURE

JOSEPH EARLE MOORE, M.D.

BALTIMORE

The following review covers the literature on syphilis for 1934 and the first six months of 1935. A few of the more important papers appearing in 1933 have also been cited, particularly when necessary for the sake of continuity. In view of the large number of titles involved (the "Quarterly Cumulative Index Medicus" for 1934 lists 932 titles under the heading syphilis alone, not including those listed under drugs, organs, *Spirochaeta pallida* and diseases such as aortitis, neurosyphilis, dementia paralytica and tabes dorsalis), it has been necessary to exercise a rather rigid selection. Except for one important article with clinical applications, almost all reference to the serodiagnosis of syphilis has been omitted. In the field of experimental syphilis relatively few articles have been mentioned. In the more purely clinical field preference has been given to articles in the English and American literature, though I believe that the more important German and French literature also has been adequately covered. An attempt has been made to include also reference to articles which provide an adequate bibliography of the subject covered.

HISTORY OF SYPHILIS

Reawakened interest in the history of syphilis is apparent in a number of recent papers which do not lend themselves to review but which must be listed in a general summary of the subject. The more important of these articles are those by Holcomb,¹ Butler and Biello,² Moore and Solomon,³ Zimmermann,⁴ Klein⁵ and Hendrickson.⁶

From the Syphilis Division of the Medical Clinic of the Johns Hopkins Hospital.

1. Holcomb, R. C.: Christopher Columbus and the American Origin of Syphilis, U. S. Nav. M. Bull. **32**:401, 1934.

2. Butler, C. S., and Biello, J. A.: The Influence of Ruy Diaz de Isla upon the Question of the American Origin of Syphilis, South. M. J. **26**:438, 1933.

3. Moore, M., and Solomon, H. C.: Contributions of Haslam, Bayle, and Esmarch and Jessen to the History of Neurosyphilis, Arch. Neurol. & Psychiat. **32**:804 (Oct.) 1934; Contributors to the History of Syphilis of the Nervous System: Ulrich von Hutten (1488-1524), Arch. Dermat. & Syph. **31**:692 (May) 1935.

(Footnotes continued on next page)

SPIROCHAETA PALLIDA

In an interesting article, which is particularly valuable to the English and American reader for its bibliography, Bessemans and his associates⁷ discuss a wide variety of experimental facts bearing on the question of an invisible form of *Spirochaeta pallida*. The bibliography contains, in addition to references on this subject, a practically complete list of Bessemans' own work on many related topics, particularly in the field of experimental pyretotherapy.

The authors point out that the evidence for the existence of a life cycle of the spirochete, including some phase other than the spiral form, rests (1) on the demonstration, especially by silver staining methods and in tissues, of granules and of apparent transitional forms between these and the typical spiral forms; (2) on the seeming incongruity between the infectious potency of tissues (especially lymph nodes) from experimental animals and the extreme difficulty of demonstrating spirochetes in these organs, and (3) on the observations of Levaditi and his associates⁸ that when implants of syphilitic tissue are made in rabbits, these grafts pass through a "prespirochete phase," or initial pause, during which no spiral form is present, and then suddenly, with no apparent transition, enter on a phase in which numerous typical spirochetes are present.

Bessemans and his group, however, believing with others that the available evidence does not justify conclusions as to the existence of a granular form of spirochete, have performed a series of experiments the results of which may be summarized as follows:

The incubation period of the chancre is somewhat lower in rabbits and guinea-pigs inoculated with syphilitic tissues (lymph nodes, spleen and brain) in which spirochetes can be demonstrated only with difficulty or not at all than when the inoculum is spirochete-rich testicular syphiloma. When these various tissues are progressively diluted, the infec-

4. Zimmermann, E. L.: The Pathology of Syphilis as Revealed by Autopsies Performed Between 1563 and 1761, *Bull. Inst. Hist. Med.* **3**:355, 1935.

5. Klein, J. E.: LeClerc's Account of the Origin of Chemotherapy and the Introduction of Syphilis into Europe, *Arch. Dermat. & Syph.* **31**:324 (March) 1935.

6. Hendrickson, G. L.: The "Syphilis" of Girolamo Fracastoro, with Some Observations on the Origin and History of the Word "Syphilis," *Bull. Inst. Hist. Med.* **2**:515, 1934; in *Bull. Johns Hopkins Hosp.*, November 1934.

7. Bessemans, A.; van Haelst, J., and DeWilde, J.: An Experimental Study of the Problem of the Existence of an Invisible Form of the Syphilitic Virus, and of Spontaneous Spirochetosis in Rabbits, *Am. J. Syph. & Neurol.* **19**:161, 1935.

8. Levaditi, C.; Vaisman, A.; Schoen, R., and Mezzer, J. G.: Cycle évolutif du virus syphilitique; neurosyphilis; virulence du *T. Pallidum*, *Ann. Inst. Pasteur* **50**:222, 1933.

tiousness of transplants of tissue from a popliteal lymph gland is from ten to fifty times weaker than that of tissue from testicular syphilomas. Spirochetes can always be demonstrated by dark-field examination in organs (lymph nodes) in which they have heretofore been found with great difficulty or not at all provided an appropriate technic is employed. With an ingenious mathematical formula it is possible even to calculate the approximate number of spirochetes in any organ. Utilizing this count, the authors have demonstrated a direct relationship between the number of spirochetes in a graft and the promptness of appearance of lesions following its transplantation; and they express the belief that by progressive dilution of tissues they can produce infection as long as a single spirochete (from lymphatic tissue) remains and that infection fails when the spiral form of the spirochete has finally disappeared (through dilution). The virus in lymph nodes is apparently of much greater virulence than that in testicular syphilomas, since fewer spirochetes are needed to infect with the former than with the latter tissue and since their thermoresistance is greater in lymphoid tissue. On the basis of these facts the authors state that there is no necessity for assuming the existence of a granular or invisible form of the virus and that the only infectious agent of syphilis is the visible spirochete.

Nyka⁹ presents the opposite point of view. Clinically, it has been for a long time remarked that the disappearance of spirochetes, whether spontaneous or accelerated by treatment, is not synonymous with cure. On the contrary, the gravest complications often occur when one can no longer find spirochetes in the body. Two hypotheses may explain these facts: Either these complications are produced by some virus other than that of the spirochete or spirochetes can exist in some other form than the classic one. Schaudinn himself expressed belief in the second hypothesis, and a serious basis for that hypothesis was found in the work of Jacquet and Sézary¹⁰ and of Levaditi, Schoen and Sanchis-Bayarri. Both of these groups of workers demonstrated totally different forms from the classic spirochete, ranging by intermediate stages to argentaffin granules of small dimensions. Numerous workers have noted that certain organisms, particularly those in the lymph nodes of rabbits, were virulent for normal animals, although spirochetes could not be demonstrated. However, a number of investigators and finally van Haelst¹¹ have demonstrated spirochetes in small numbers in these glands. Similar observations have been made on the mouse. There is, however, a marked contrast between the very small number of demonstrable organisms in these organs and often their total absence and, on the other

9. Nyka, W.: Le virus syphilitique: ses variations morphologiques, sa multiplication, et son action pathogène, *Ann. Inst. Pasteur* **53**:243, 1934.

10. Jacquet and Sézary: *Bull. et mém. Soc. méd. d. hôp. de Paris* **24**:114, 1907

11. van Haelst: *Compt. rend. Soc. de biol.* **113**:1535, 1933.

hand, their great virulence. In order to explain this phenomenon, Levaditi and his collaborators undertook a series of experiments which led them to express their belief in the existence of granular forms of the spirochete. This theory, however, has not been entirely accepted. The suggestion that the unknown form of the spirochete may be an ultra-virus implies filtrability. However, no one has yet been able to demonstrate this feature.

Nyka states that by a series of experiments he has demonstrated the following facts: 1. The organism of syphilis has two distinct morphologic aspects—the spirochete and a filamentous form, with all grades of transitional forms between these two. 2. The transmission of syphilis is by the spirochetal form, the rôle and existence of which are ephemeral. The spirochetal form disappears once the infection is established in the new host. 3. The filamentous form constitutes the usual form of syphilitic virus in the body, and to it is to be attributed the characteristic pathologic picture of syphilis. 4. The change of morphologic form does not involve any modification of the biologic properties of the parasite. 5. In the spirochetal form the parasite can penetrate into cells and multiply in their interior, either in the cytoplasm or in the nucleus. As soon as it penetrates the interior of a cell it loses its spiral form and becomes a filament. This transformation can also occur outside the cell. The author maintains that he has continually seen this occur under the dark-field microscope. He has studied in this way a suspension of syphiloma in Ringer's solution mixed with equal parts of a suspension of mouse spleen and chicken embryo juice. 6. In its filamentous form the parasite can multiply by transverse division, and the filaments resulting from this division can be transformed again into spirochetes. 7. The multiplication of the parasite in the interior of a cell is not compatible with the survival of the cell. 8. All cells of the body do not present the same degree of vulnerability to syphilitic virus. Hepatic cells and fibroblasts are least sensitive; lymphoid cells and those of the nervous system are highly sensitive. 9. In the filamentous form the syphilitic virus has not heretofore been seen because of its feeble staining properties.

In addition to the dark-field studies Nyka has studied by silver impregnation methods tissue from infected rabbits, particularly lymph nodes, testicular syphilomas, spleen and liver, and from infected mice, particularly lymph nodes, liver and brain. To me his illustrations do not seem to be particularly convincing since he himself states that they do not lend themselves well to demonstration to others because of the precipitation of silver granules in many albuminous materials. He does not seem to have controlled his study by the examination of tissue from normal animals.

Gastinel and Pulvenis¹² have also studied one phase of the subject with the method used by Bessemans: the inoculation of rabbits with constantly increasing dilutions of syphilitic virus. As the concentration decreases the period of incubation lengthens, though the character of the lesion remains unchanged. When the amount of testicular emulsion was decreased below 0.001 cc., however, symptomless infection occurred (with amounts as small as 0.0005 cc.).

Morgan and Thomas¹³ attempted to determine the minimum infective dose of spirochetes by using the Barbour single cell technic. While the method employed is not above criticism, they were unable to obtain successful inoculations of rabbits, symptomless or otherwise, by means of the intratesticular inoculation of from one to six spirochetes.

Culture of S. Pallida.—As a result of personal experiments and of a thorough survey of the literature, Kast and Kolmer¹⁴ conclude that it is highly doubtful if any investigator has succeeded in cultivating on artificial mediums virulent forms of *S. pallida*. In this opinion Plaut¹⁵ and Jahnelt¹⁶ concur; indeed, Jahnelt has failed not only with his own material but with cultures supplied him by other investigators who have claimed success. He was able to continue subcultures by various methods, but these were invariably avirulent.

Hoffmann and Frohn¹⁷ claimed (alas, prematurely) that they had succeeded in obtaining pure cultures of *S. pallida* directly and immediately from closed testicular chancres of rabbits, utilizing Kroon's liquid nutritive medium. Subcultures were carried through five passages and were still virulent for rabbits at the end of that time. In a later paper, however, Hoffmann¹⁸ joins the ranks of the skeptics and reports his

12. Gastinel, P., and Pulvenis, R.: Du rôle de la quantité de virus dans la syphilis expérimentale du lapin; la dose-seuil de l'infection inapparente, Bull. Soc. Franç. de dermat. et syph. **41**:330, 1934.

13. Morgan, H. J., and Thomas, C. S.: Single Cell Inoculations with *T. pallidum*, J. Exper. Med. **59**:297, 1934.

14. Kast, C. C., and Kolmer, J. A.: On the Cultivation of *S. Pallida* in Living Tissue Media, Am. J. Syph. & Neurol. **17**:529, 1933.

15. Plaut, F.: Ueber das Fehlen der antigenen Funktion der Gewebespallidiae im Gegensatz zu der antigenen Wirksamkeit der in Reinkultur gezüchteten Syphilis-spirochäten, Ztschr. f. Immunitätsforsch. u. exper. Therap. **81**:479, 1934.

16. Jahnelt, F.: Untersuchungen über das Verhalten der Pathogenität von Spirochäten auf künstlichen Nährböden, insbesondere über die willkürliche Beeinflussung der Pathogenität von Hühnerspirochätenkulturen, Zentralbl. f. Bakt. (Abt. 1) **130**:349 (Dec. 29) 1933; Lässt sich die *S. pallida* auf künstlichen Nährboden kultivieren? Klin. Wchnschr. **13**:550, 1934.

17. Hoffmann, E., and Frohn, W.: Ueber Gewinnung einer direkten virulenten Reinkultur der *S. pallida* aus Kaninchensyphilom in flüssigem Nährboden, Klin. Wchnschr. **13**:206, 1934.

18. Hoffmann, E.: Gewinnung einer virulenten Reinkultur der Spirochaeta Pallida aus Kaninchensyphilom: Nachtag, Klin. Wchnschr. **13**:1540, 1934.

own inability to obtain further positive results with his original culture in generations later than the fifth, and also that he was not able to obtain further pure cultures from other closed syphilomas. He expresses the belief that his report of success in culturing virulent spirochetes was too hastily made and was a mistake, and agrees with those who believe that true cultures of *S. pallida* have never been obtained. Similar claims have from time to time been made by other investigators, beginning with Noguchi, the flaw being that on repetition in a different laboratory failure has always resulted.

THE CELLULAR PATHOLOGY OF SYPHILIS

Cunningham and his associates¹⁹ in a series of stimulating papers have applied to the study of experimental syphilis the supravital method, which they previously employed with Sabin in studies on tuberculosis. They observed that the lesions of experimental syphilis in the rabbit contain higher numbers of phagocytic mononuclear cells (clasmatoocytes, macrophages) and that the epithelioid cells present in tuberculous lesions are absent in syphilitic lesions. The clasmatoocytes are much more numerous and much more phagocytic than in normal animals. It is apparently possible to increase still further the phagocytic activity of these cells in experimental animals by the intravenous administration of either trypan blue or lecithin. These substances, not in themselves spirocheticidal, nevertheless foster the resolution of syphilitic lesions in rabbits and inhibit the development of metastatic lesions. The authors suggest the hypothesis that the mechanism of resolution of syphilitic lesions may reside in the phagocytic activity of the large mononuclear cells of the tissues. It is hoped that this work will be continued, since it offers a new and promising theory of the pathologic aspects, course, progress and treatment of syphilis.

The Blood in Syphilis.—Spangler²⁰ observed moderate eosinophilia in the blood of approximately 40 per cent of his syphilitic patients. He believes that this indicates the development of an allergic cellular mechanism of defense. He also is of the opinion that in a nonallergic person without intestinal parasites the presence of a moderate degree of eosino-

19. Cunningham, R. S.; Morgan, H. J.; Tompkins, E. H., and Harris, S., Jr.: The Cellular Pathology of Experimental Syphilis as Studied by the Supravital Method, *Am. J. Syph. & Neurol.* **17**:515, 1933. Harris, S., Jr.; Tompkins, E. H.; Morgan, H. J., and Cunningham, R. S.: The Effect of Lecithin on Experimental Syphilis in the Rabbit, *ibid.* **18**:333, 1934. Morgan, H. J.; Harris, S., Jr.; Tompkins, E. H., and Cunningham, R. S.: The Effect of Trypan Blue on Experimental Syphilis in the Rabbit, *ibid.* **17**:522, 1933.

20. Spangler, R. H.: Eosinophilia in Syphilis: Comparative Study of Differential Leucocyte Counts in One Hundred Positive and One Hundred Negative Blood Wassermann Cases, *J. Lab. & Clin. Med.* **20**:733, 1935.

philia, especially if associated with lymphocytosis, should serve as a diagnostic suggestion of the presence of syphilis and should prompt careful search for clinical and laboratory evidence of syphilis.

Continuing the studies of Cunningham and his associates on the essential cellular response of the blood and tissues in experimental syphilis, Lowenstein²¹ has studied the leukocytic formula in the early acute stage of experimental syphilis in rabbits. He observed an increase in the number of phagocytic mononuclear cells, which qualitatively showed evidence of increased physiologic and phagocytic activity. There was also a decrease in the number of lymphocytes. The degree of increase of the phagocytic mononuclear cells paralleled the degree of activity at the site of the testicular lesions. No significant changes were observed in the total number of leukocytes or in other elements of the differential blood count.

In a series of papers Rosahn, Pearce and Casey²² report their studies of the cytology of the blood of syphilitic animals and human beings. In rabbits during the period of active disease there was an increase in the total leukocyte count and in the number of neutrophils, monocytes and platelets and a decrease in the number of lymphocytes. During the period of latency these changes in the leukocytes disappeared, but a mild secondary anemia developed. There is a distinct parallelism between these observations and those made on human beings. In early syphilis in human beings there are mild leukocytosis; an increase in the number of monocytes, neutrophils and platelets and a decrease in the number of lymphocytes. In late syphilis these changes disappear, but a moderate or marked anemia is frequently observed. All these changes tend to disappear following treatment.

SEROLOGY

The American Serologic Conference.—Under the combined auspices of the United States Public Health Service and the American Society of Clinical Pathologists a competitive conference of American serologists has just been held²³ for the purpose of determining the reliability

21. Lowenstein, L.: The Leucocytes in Early Acute Experimental Syphilis in Rabbits, *Am. J. Syph. & Neurol.* **19**:39, 1935.

22. Rosahn, P. D., and Pearce, L.: The Blood Cytology in Untreated and Treated Syphilis, *Am. J. M. Sc.* **187**:88, 1934. Rosahn, P. D.; Pearce, L., and Casey, A. E.: Observations on the Blood Cytology in Experimental Syphilis: I. The Period of Disease Activity, *J. Exper. Med.* **59**:711, 1934. Rosahn, P. D.: Observations on the Blood Cytology in Experimental Syphilis: II. The Period of Disease Latency, *ibid.* **59**:721, 1934.

23. Cumming, H. S.; Hazen, H. H.; Sanford, A. H.; Seneor, F. E.; Simpson, W. M., and Vonderlehr, R. A.: Evaluation of Serodiagnostic Tests for Syphilis in the United States, *J. A. M. A.* **103**:1705 (Dec. 1) 1934; Evaluation of Serodiagnostic Tests for Syphilis in the United States: Report of Results, *ibid.* **104**:2083 (June 8) 1935.

of the several serodiagnostic methods that are in common use in this country. The conference was organized in the same manner as earlier international competitions in Europe and South America, except that in this instance the participating serologists worked in their own laboratories rather than in a central place. Twelve hundred specimens of blood and of spinal fluid from carefully selected donors were examined under identical conditions by fourteen participating serologists, four of whom (Brem, Kolmer, Ruediger and Williams) performed some modification of the complement-fixation (Wassermann) test and ten of whom (Eagle, Hinton, Johns, Kahn, Kline, Kurtz, Lufkin and Rytz, Rein and Weiss) performed a flocculation test. Detailed descriptions of the technic employed by each of these workers will appear in a subsequent communication. Specimens of blood were submitted (1) from patients with untreated primary syphilis, (2) from patients with untreated secondary syphilis, (3) from patients with late syphilis both treated and untreated, (4) from normal, presumably nonsyphilitic persons and (5) from presumably nonsyphilitic patients with leprosy, tuberculosis, cancer, fever, malaria and jaundice, pregnant women and normal women both during menstruation and in the interim. Samples of spinal fluid were submitted in equal numbers from neurosyphilitic and nonsyphilitic patients.

The conference scored the tests of the competing serologists on two bases: (1) sensitivity, i. e., the proportion of positive results in about 400 patients with known syphilis, and (2) specificity, i. e., the percentage of false positive (not including false doubtful) reactions secured in 152 presumably normal controls. I believe, however, that specificity might be more accurately determined if there were added to the 152 normal controls the approximately 300 presumably nonsyphilitic persons with the other conditions listed in the preceding paragraph (excluding, for reasons which will presently appear, leprosy and malaria) and if to false positive results in this heterogeneous group were also added false doubtful reactions (which can cause as much confusion in the mind of the clinician). Refigured on this basis the most satisfactory tests on both scores, i. e., sensitivity and specificity, were the complement fixation (Wassermann) test performed by Ruediger and the Kline diagnostic flocculation test as performed by Kline. A close second was the standard diagnostic Kahn flocculation test as performed by Kahn. Equally close thirds were the Eagle flocculation test and the Kahn presumptive flocculation test (Kurtz). The others were relatively unsatisfactory on one score or the other.

It is of interest to note that in specimens from presumably nonsyphilitic patients with leprosy or malaria all of the competing serologists obtained a significantly higher proportion of positive results than in specimens from patients with other nonsyphilitic conditions. In speci-

mens from persons with leprosy the percentage of positive results ranged from 44 to 72, and in those from persons with malaria, from 8 to 20. It seems reasonable to conclude, therefore, that leprosy often and malaria occasionally may cause a false positive serologic test for syphilis. The uniformity of the results should aid in settling the controversy that has raged around the question in these two diseases.

The evaluating committee state as their conclusion that there is relatively equal value to the clinician of efficient complement-fixation and efficient flocculation tests as performed on specimens of either blood or spinal fluid. If two tests are performed as an intralaboratory check, it is immaterial whether two complement-fixation tests, two flocculation tests or one of each is chosen. There is some evidence that a properly performed highly sensitive flocculation test might be used as a routine procedure for the purpose of excluding the likelihood of the presence of syphilis. If a negative result is obtained by such a method, it is likely that it will be negative by any other method. If the test yields a positive result, it should be repeated and compared with one or more highly specific flocculation or complement-fixation tests. The committee recommend the uniform adoption of the words positive, doubtful and negative in reporting tests in place of the various plus marks at present in common use.

The Relationship Between Serologic Tests of the Blood and Those of the Spinal Fluid.—The routine use of lumbar puncture during the treatment of patients with early and late syphilis is insisted on by all modern American syphilologists. Asymptomatic neurosyphilis is common; it is the forerunner of subsequent clinical involvement; abnormalities of the cerebrospinal fluid may be present when the Wassermann reaction of the blood is negative. These abnormalities do not depend on the passage of reagin from the blood to the spinal fluid but are elaborated locally in the nervous system, and in the experience of most serologists and clinicians no serologic test of the blood has as yet been devised that is so sensitive as to be always positive when the cerebrospinal fluid is abnormal. It is unfortunate, therefore, that on the basis of insufficient evidence Hinton²⁴ claims that the test which he has devised is sufficiently sensitive. On the basis of studies of only 50 patients with early syphilis for whom both Hinton tests and examinations of the cerebrospinal fluid were made at the same time, he concludes that in order to demonstrate the presence of asymptomatic neurosyphilis lumbar puncture is not necessary during the first two years of the disease, since in his patients the examinations of the spinal fluid and the Hinton tests were negative in 20 instances and no positive reac-

24. Hinton, W. A.: Hinton Test and Lumbar Puncture in Treated Primary and Secondary Syphilis, *Arch. Dermat. & Syph.* **30**:813 (Dec.) 1934.

tion of the spinal fluid was observed when the Hinton test was negative, though in 2 such instances the results of the tests of the spinal fluid were doubtful. His conclusion is obviously unjustified on the basis of such meager data, and the publication of this paper may do a great deal of harm by persuading uncritical physicians that a study of the cerebrospinal fluid is unnecessary.

Cerebrospinal Fluid.—Solomon, Dailey and Fremont-Smith²⁵ present a valuable study and simple formulas whereby a reasonably accurate cell count, values for protein, sugar and chloride content and colloidal reactions may be obtained on cerebrospinal fluid that has been accidentally contaminated with blood.

The Kahn test on the cerebrospinal fluid was found by Loveman and Stocking²⁶ to be unreliable when as little as 0.0018 cc. of blood serum giving a strongly positive Kahn reaction was added to 6 cc. of spinal fluid. These authors conclude that if the Kahn test of the cerebrospinal fluid is positive and the fluid has been contaminated with blood, another lumbar puncture should be done. It has been my experience with the Wassermann test, however, that this precaution is often unnecessary if the quantitative Wassermann titer of the blood serum at the time of the lumbar puncture is known.

The Luetin Test and Cutaneous Allergy in Syphilis.—After the introduction of the luetin test by Noguchi in 1911, a controversy as to its value ensued. This controversy died down when the original test was shown to be of no practical value but was renewed with the relatively recent interest in "organic luetin." The latest careful study by Barker²⁷ shows once more that luetin of any type is of no practical value in diagnosis or as a determination of cure. Its status in treatment is not settled, but its value is not great.

Bessemans, Dujardin and Wiser²⁸ have conducted a more elaborate and better controlled study of several extracts of luetin which they have prepared. Their conclusions are of great interest to the student of the influence of immunity and of constitution in determining the response to syphilitic infection. Cutaneous reactivity to these various extracts is at its height in patients with allergic lesions of tertiary syphilis and at

25. Solomon, P.; Dailey, M. E., and Fremont-Smith, F.: Contamination of the Cerebrospinal Fluid by Blood, *Arch. Neurol. & Psychiat.* **31**:1222 (June) 1934.

26. Loveman, A. B., and Stocking, L.: Kahn Reaction with Spinal Fluids Containing Varying Amounts of Syphilitic Blood, *Arch. Dermat. & Syph.* **29**:653 (May) 1934.

27. Barker, L. P.: Value of Organic Luetin in Diagnosis and Treatment of Syphilis, *Arch. Dermat. & Syph.* **30**:676 (Nov.) 1934.

28. Bessemans, A.; Dujardin, B., and Wiser, M.: Sur l'hypersensibilité cutanée des syphilitiques, *Ann. de dermat. et syph.* **4**:1010, 1933.

its minimum in those with parasyphilis (i. e., parenchymatous neurosyphilis). It may be shown in response to the intradermal injection of not only extracts of luetin but of various protein products, such as horse serum or cow's milk. It is more striking in women than in men, corresponding to the milder course of syphilis in women. These workers agree, however, that skin testing of this sort is of no value in diagnosis. To me it seems to offer a prolific field for further investigation with regard to immunity and constitution in order to determine the probable course of syphilis in a freshly infected person.

THE EPIDEMIOLOGY OF SYPHILIS

Usilton²⁹ provides a valuable summary of the surveys that have been made of the prevalence of venereal disease in recent years by the United States Public Health Service and the American Social Hygiene Association with the cooperation of state and local health authorities. Forty-nine representative communities, with a total population of approximately 29,000,000 persons, are included. As far as syphilis is concerned, there are constantly under medical care for this disease 4.3 persons per thousand population, an approximate total of 683,000 persons. The annual incidence of fresh infections with syphilis is 4 per thousand. The trend of the incidence of syphilis appears to be upward, with a possible 3.4 per cent increase during the past period of from three to six years.

In contrast to this gloomy state of affairs in this country is the fact that in Denmark syphilis is disappearing. In 1933 only 700 fresh infections occurred in the entire country (population of 3,500,000), an incidence rate of 0.2 per thousand. Had the incidence rate in Denmark been the same as in the United States, 14,000 new cases would have been reported instead of a mere 700. The measures which epidemiologists agree have accomplished this striking decrease in incidence are described in illuminating papers by Kissmeyer³⁰ and Lomholt.³¹

Smith and Brumfield³² have provided a useful demonstration of the practicability and value of tracing the sources of contact of persons infected with syphilis. This type of "shoe leather" epidemiology is of the highest importance from the standpoint of public health.

29. Usilton, L. J.: Trend of Syphilis and Gonorrhea in the United States, Based on Treated Cases, *Ven. Dis. Inform.* **16**:147, 1935.

30. Kissmeyer, A.: Sur la quasi-disparition de la syphilis au Danemark, *Bull. Soc. franç. de dermat. et syph.* **40**:926, 1933.

31. Lomholt, S.: Rückgang der Syphilis in Dänemark 1919-1933, *Dermat. Wchnschr.* **100**:173, 1935.

32. Smith, D. C., and Brumfield, W. A., Jr.: Tracing the Transmission of Syphilis, *J. A. M. A.* **101**:1955 (Dec. 16) 1933.

DRUGS

Mercury.—Sollmann, Schreiber, Cole and their collaborators³³ have continued their studies on the absorption and excretion of mercury. The important conclusions are found in the second paper cited. The anti-syphilitic efficiency of mercurial treatment appears to be conditioned on the continued maintenance of an adequate concentration of diffusible, dissociable mercury. The mercury that is fixed and stored in the tissues appears to play no therapeutic rôle. The urinary excretion of mercury serves as an indicator of the presence of diffusible mercury. With therapeutically effective preparations and routes of administration, excretion is continuously cumulative. All forms of treatment yielding levels below 0.5 mg. of mercury per day at the end of the fourth week are clinically ineffective. These include inunction with ointments of mild mercurous chloride and with weak (5 per cent) ointments of metallic mercury and mercury oleate; oral administration of mercuric chloride in doses of 15 mg. per day; intravenous injection of the oxycyanide and intramuscular injection of the benzoate in the usual dosage; intermittent intramuscular injection of biniodide, and intravenous injection of compounds with their mercury in firm organic combination—salyrgan, novasurol and mercurosal. These give very high temporary levels for the excretion of mercury, but they sink to insignificant ones within a few hours. All methods of treatment which secure a daily urinary excretion of from 0.8 to 1 mg. of mercury at the end of the fourth week are effectively antisypilitic and may cause stomatitis. The ordinary and the massive inunctions, the daily oral administration of 0.2 Gm. of mercury with chalk, the daily intramuscular injection of mercuric sodium bromide and the weekly intramuscular injection of mercuric oil come within this group. With the last preparation there is the constant danger of cumulative intermittent absorption and intoxication. All of these methods, however, may be dangerous. Considerable quantities of mercury are retained in the body indefinitely, but this retained mercury is therapeutically useless and may be harmful.

These studies represent an enormous amount of painstaking careful work. It seems regrettable that this effort is robbed of much of its importance by the nearly complete abandonment of mercury in favor of bismuth in clinical practice.

33. Sollmann, T.; Schreiber, N. E.; Cole, H. N., and others: Excretion of Mercury After Oral Administration of Mercury with Chalk, Yellow Mercurous Iodide and Corrosive Mercuric Chloride, *Arch. Dermat & Syph.* **31**:15 (Jan.) 1935; Excretion of Mercury After Clinical Intramuscular and Intravenous Injections, *ibid.* **32**:1 (July) 1935.

Bismuth.—In a comprehensive review documented by a bibliography of 204 references, Levaditi ³⁴ brings up to recent date (1932) the status of bismuth in the treatment and prophylaxis of syphilis. He covers the history of the drug, enumerates and describes the preparations in common use in the United States as well as abroad, and considers toxicity, tolerance, the pathogenesis and pathology of bismuth intoxication, the absorption of bismuth and its distribution in the tissues, the therapeutic effect and mechanism of its action, the accidents and reactions of bismuth therapy and the prophylaxis of syphilis by means of this drug.

He favors for clinical use the liposoluble alpha-carboxethyl-beta-methylnonoate (marketed in this country as biliposol), which he says acts almost as rapidly as the arsphenamines; and he makes the assertion, with which few investigators outside France will agree, that syphilis can be treated exclusively with this drug, with results equivalent to those obtainable with the arsphenamines.

Bismuth Prophylaxis of Syphilis.—In 1926 Kolle and Evers reported interesting experiments in which they injected the very insoluble bismuth oxychloride into a rabbit's ear or thigh and then a few days later inoculated the animal intratesticularly with syphilitic virus. They observed the animals over a period of several months, and no chancre appeared. Then they surgically removed the remaining deposit of bismuth, whereupon a chancre promptly developed at the point of inoculation. They therefore concluded that the action of bismuth was spirochetistatic rather than spirocheticidal; i. e., it prevented the growth of the virus rather than destroyed it. This important work had not been repeated until Levaditi and his collaborators ³⁵ undertook it. They demonstrated that when insoluble metallic bismuth was used it was impossible to administer to rabbits an adequate prophylactic dose capable of complete surgical removal, but when a liposoluble salt was employed the animals were completely protected against infection, both before and after the surgical removal of the deposit of bismuth. This protection was manifest by the absence of a chancre at the site of inoculation, by negative results of the transfer of material from the lymph nodes and by the ultimate susceptibility of the animals (after removal of all the bismuth either surgically or by normal excretory processes) to reinoculation. They conclude that when bismuth is given in adequate form and in sufficiently large doses it is actually spirocheticidal rather than spirochetistatic. The

34. Levaditi, C.: Etat actuel de la bismuthothérapie et de la bismuthoprévention de la syphilis, *Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap.* **14**: 297, 1933.

35. Levaditi, C.; Hornus, G.; Vaisman, A., and Manin, Y.: Mécanisme de l'action préventive exercée par le bismuth dans la syphilis expérimentale, *Bull. Acad. de méd., Paris.* **112**:306, 1934.

different results obtained by Kolle and Evers are apparently due only to the extreme insolubility and low absorbability of the bismuth preparation which they employed.

Oral Administration of Bismuth.—In a series of four papers Serefis and Mulzer³⁶ discuss the treatment of syphilis by the oral administration of bismuth. In the first paper of the series Serefis describes the manifestations of acute and chronic bismuth poisoning and presents the results of some experiments dealing with the solubility and absorbability of different bismuth preparations. In a rather confused presentation he states that he finally settled on bismuth chloride as a suitable salt for oral administration. This preparation is completely soluble in an acid medium, but this medium is too acid for ingestion. Its relative insolubility in an alkaline medium can be overcome by the addition of certain salts, alcohols or sugars which, in the author's opinion, combine with the bismuth chloride to form complex salts of an undetermined nature.

The second paper deals with the treatment of experimental syphilis in rabbits with various bismuth compounds given by mouth. Acid bismuth chloride in glycerin was effective in rabbits when three doses of 0.172 Gm. of metallic bismuth was given. Unfortunately, the number of animals treated was small (only 7), the dosage is not expressed in milligrams per kilogram of body weight, the intervals between multiple doses are not given, the period of observation of the animals was inadequate and "cure" of the animals was not checked by the transfer of glandular tissue. In spite of these inadequate data, several patients with early syphilis were treated with a mixture of bismuth chloride, sodium citrate and glycerin in a daily dose of 0.8 Gm. of metallic bismuth, with what Serefis considered as encouraging results.

Next, in a long paper, Serefis supplies more but still inadequate details of his own experimental work. In addition to the deficiencies in his protocols that have been noted, his work is still further subject to serious criticism on the ground that he does not describe the proportions used in the most effective preparation tried, i. e., bismuth chloride plus sodium citrate plus glycerin.

On the basis of these observations, which if adequate to convince the investigators of the value of the method are so inadequately presented as to leave the reader greatly confused, Mulzer and Serefis proceeded

36. Serefis, S.: Die perorale Wismutvergiftung, *Med. Klin.* **30**:968, 1934; Die Resorptionsbedingungen des Wismut vom Magen-Darmkanal aus, *Deutsche med. Wchnschr.* **60**:1237, 1934; Ueber die Resorptionsbedingungen des Wismut und ihre Auswertung für die perorale Luestherapie, *Arch. f. Dermat. u. Syph.* **171**:1, 1934. Mulzer, P., and Serefis, S.: Die perorale Wismutbehandlung der Syphilis, *München. med. Wchnschr.* **81**:1525, 1934.

further. They treated bismuth chloride with 8 per cent liver extract (the method is not described) and obtained a substance not chemically identified but which they believed to be a complex bismuth salt, to which they gave the name "bismutrat." If the authors tried this substance on experimental animals, they do not mention it in their papers. (The manufacturers, however, state that the action of "bismutrat" in rabbits with experimental syphilis is inferior to that in human beings because of the alkaline state of the complex salt.) In spite of the absence of adequate experimentation on animals, Mulzer and Serefis used this substance on 43 patients with syphilis (13 had primary and 24 secondary syphilis). The average daily dose was from 25 to 40 Gm., thirty doses constituting a course. None of the patients died of bismuth poisoning. According to the authors, surface organisms disappeared, lesions healed and reversal of the Wassermann reaction occurred with great rapidity.

I have discussed these articles in detail because of the authority represented by the authors' names, because unjustified clinical trial preceded adequate experimentation (or at least adequate presentation of that experimentation) and because, on the basis of thoroughly inadequate evidence of the value of the method or the preparation employed, commercial distribution of "bismutrat" has already begun abroad and may shortly occur in this country.

Considerable interest in this subject has been aroused in this country also. Kolmer³⁷ reports on the oral use of water-soluble potassium bismuth tartrate in experimental animals and man. Unfortunately, his paper is devoid of protocols of his experimental work, and the reader must rely on statements only. This is, of course, a most unsatisfactory method of presentation of an important scientific subject. However, if one accepts Kolmer's statements at their face value, they are as follows: Rabbits tolerated without obvious damage fifty consecutive daily oral doses of 20 mg. (approximately 8 mg. per kilogram), rats tolerated 5,000 mg. per kilogram, given in a single dose; the daily dosage employed for adult human beings was from 0.57 to 1.2 Gm. Syphilis was apparently cured in rabbits by twenty-four daily doses of 20 mg. per kilogram. Kolmer states that he has used this method of treatment in human beings for ten years, that the bismuth compound administered orally gives better results than mercury salts given in the same manner and that there are definite indications for the use of the method in human beings.

Neither the work of Mulzer and Serefis nor that of Kolmer can as yet be accepted as justifying a clinical trial of this method. Too many details of both experimental and clinical results are lacking in the reports of these observers. It is to be hoped that the entire subject will be

37. Kolmer, J. A.; Oral Administration of Potassium Bismuth Tartrate in Treatment of Syphilis, *Arch. Dermat. & Syph.* **31:9** (Jan.) 1935.

critically restudied, with more careful and adequate reports of the results obtained.

Bismuth in the Central Nervous System.—Much of the commercial propaganda for iodobismutol has stressed the supposed power of the preparation to penetrate the nervous system and the consequent desirability of its use in neurosyphilis. The contrary results reported by Levaditi and his associates³⁸ are therefore of interest. They observed that both in therapeutic efficacy in rabbits with syphilis and in its power to penetrate the nervous system and invade the cerebrospinal fluid, iodobismutol is equal, but not superior, to other liposoluble bismuth preparations.

The excretion of iodobismutol is shown by Hanzlik, Mehrtens and Spaulding³⁹ to be largely by way of the urine and in amounts comparable to those following the use of water-soluble bismuth salts. Klauder and Brown⁴⁰ utilize these facts, together with their own failure to demonstrate an increased concentration of bismuth, in the cerebrospinal fluid of human beings and in the brains of experimental animals after the administration of iodobismutol as compared with other bismuth preparations, to refute the argument of Hanzlik and his co-workers that the particular penetrating power of iodobismutol is due to the existence of bismuth in the anionic form.

The Iodides.—Greenbaum and Cobane⁴¹ express the opinion that the only effect of the iodides in syphilis is in dissolving syphilitic exudates and incompletely organized fibroses, that these effects are better accomplished by arsenical or bismuth compounds and that there is evidence to suggest that the iodides are not indispensable in the treatment of syphilis irrespective of the stage or manifestation. While this opinion is based on hypothesis rather than on observed facts, it is identical with the point of view of other syphilologists and constitutes a useful critical approach to the existing uncertainties of antisyphilitic treatment. The actual demonstration of the lack of value of the iodides (except in providing symptomatic relief) is difficult if not impossible.

38. Levaditi, C.; Vaisman, A.; Manin, Y., and Schoen, R.: La diffusion du bismuth dans le névraxe et sa pénétration dans le liquide céphalo-rachidien, Bull. Soc. franç. de dermat. et syph. **40**:738, 1933.

39. Hanzlik, P. J.; Mehrtens, H. G., and Spaulding, J. B.: Iodobismutol: Clinical Excretion of Bismuth, Arch. Dermat. & Syph. **29**:298 (Feb.) 1934.

40. Klauder, J. V., and Brown, H.: Question of Bismuth Penetration of the Nervous System: Report of Clinical and Laboratory Study, Arch. Dermat. & Syph. **29**:351 (March) 1934.

41. Greenbaum, S. B., and Cobane, J.: Syphilitic Fibrosis and the Status of the Iodides in the Present Day Treatment of Syphilis, Am. J. Syph. & Neurol. **18**:289, 1934.

TOXIC REACTIONS DUE TO DRUGS

The Effect of Antisyphilitic Treatment on Renal Function,—Sézary and Lenègre⁴² have studied the renal function of 50 untreated patients with secondary syphilis, and in 32 of these patients they have repeated the examinations after three courses of treatment with various drugs, including neoarsphenamine, insoluble and oil-soluble bismuth and mercury. In addition to careful and repeated examinations of the urine, the excretion of phenolsulphonphthalein and Ambard's constant were studied in each case. In their series of patients neither syphilis nor anti-syphilitic treatment produced any evidence of impairment of the renal function, though during treatment of any sort abundant hyaline casts could be found in the urine of almost every patient. In an additional 60 patients who had been receiving antisyphilitic treatment for periods ranging from one and a half to sixteen years, similar examinations carried out *after* (but not controlled by examinations *before* and *during*) treatment revealed in some patients the presence of mild nephritis, but it could not be clearly connected with the antisyphilitic treatment.

Ocular Damage Due to Arsphenamine.—In spite of earlier controversy on the point, recent opinion has held that although the pentavalent arsenical drugs (sodium arsinate, tryparsamide) may produce damage to the optic nerves, the trivalent arsphenamines never do. That this opinion deserves restudy is evident from the interesting report of Skirball and Thurman.⁴³ These workers observed that in 20 patients, 19 of them with early syphilis, optic neuritis developed following the administration of an arsphenamine. In some patients there were retinal hemorrhages, haziness of the vitreous and central scotomas. The authors express the opinion that the condition can be readily differentiated from the neuroretinitis of acute meningeal neurosyphilis, though they do not describe the differential points. None of their patients showed any other evidence of neurosyphilis, and in the only 3 cases tested the cerebrospinal fluid was normal. They state that the reaction occurred in the surprisingly high total of 2.7 per cent of all patients with early syphilis who were treated. The first signs are usually subjective and unilateral. Objective evidence of haziness of the vitreous or blurring of the nerve head, either absent or slight at the onset of symptoms, occurs within

42. Sézary, A., and Lenègre, J.: Le fonctionnement rénal des syphilitiques secondaires; l'action du traitement d'attaque sur le fonctionnement rénal des syphilitiques secondaires; l'action des traitements antisyphilitiques prolongés sur le fonctionnement rénal, Bull. et mém. Soc. méd. d'hôp. de Paris **49**:1278, 1280 and 1287, 1933.

43. Skirball, J. J., and Thurman, F. M.: Ocular Reactions Due to Arsphenamine, Am. J. Syph. & Neurol. **19**:197, 1935.

from a few days to two weeks. If the use of arsphenamine is continued after the reaction first appears, the condition grows progressively worse, resulting in severe optic neuritis and ending in secondary atrophy. On the other hand, if the use of arsphenamine is discontinued there is prompt improvement and in most instances complete recovery. In some instances (2 cases are cited) the same condition may be reproduced after recovery by the further administration of arsphenamine. A somewhat similar case is reported by Juler.⁴⁴

These reports are, of course, completely contrary to the experience of syphilologists and ophthalmologists the world over. While neuroretinitis does occur during or after the inadequate treatment of early syphilis (almost never in late syphilis), it has been interpreted by most observers as an ocular recurrence or neurorecurrence that is frequently associated with abnormalities in the spinal fluid that are typical of syphilis and can be cured rapidly by the administration of more arsphenamine, not by its withdrawal. It seems incredible that for twenty-five years many competent observers in clinics where this point of view prevails could have failed to note the presence of optic neuritis followed by secondary optic atrophy in 2.5 per cent of all patients with early syphilis treated with arsphenamine. Nevertheless, the subject is deserving of further careful study.

Hemorrhagic Encephalitis Due to Arsphenamine.—Glaser and the Imermans⁴⁵ report 3 of their own cases on hemorrhagic encephalitis due to arsphenamine and analyze 155 instances cited in the literature (unfortunately, the bibliography is provided only in the author's reprints). They conclude that reactions involving the nervous system appear about once in every 5,400 patients treated and once in every 29,000 injections. (On the basis of my own experience, I believe that these figures are much too high.) The mortality is about 75 per cent. The appearance of the reaction is not related to the age or sex of the patient, to the stage of the disease or to the dose of the drug. The onset of symptoms is usually from twelve hours to six days following treatment and usually early in the course of treatment. The outstanding symptoms are headache, vomiting, nervousness, chills and vertigo, with physical signs of fever, cyanosis, convulsions, changes in the pupillary reflexes and in the ocular muscles, loss of sphincteric control, hemiparesis and rigidity of the neck. The pressure of the spinal fluid is usually increased, and there is often concomitant acute nephritis. Therapy is unsatisfactory.

44. Juler, F.; Blindness After Neoarsphenamine, *Brit. M. J.* 2:809, 1934.

45. Glaser, M. A.; Imerman, C. P., and Imerman, S. W.: So-Called Hemorrhagic Encephalitis and Myelitis Secondary to Intravenous Arsphenamine, *Am. J. M. Sc.* 189:64, 1935.

In reporting 3 cases of this grave complication of treatment in pregnant women Plass and Woods⁴⁶ point out that this (and certain other serious reactions to arsphenamine) are more prone to occur in pregnant women than in other subjects.

Chetverikov and Kavyrshin⁴⁷ add reports of 3 cases of hemorrhagic encephalitis to the already voluminous literature on this subject. Their report is chiefly remarkable for the fact that all 3 of their patients survived and for some bizarre theorizing as to the relationship of this reaction to defective functioning of the vegetative endocrine apparatus, the hemato-encephalic barrier and menstruation.

Osterberg and Kernohan⁴⁸ have observed arsenic in the brain in relatively large amounts in patients with hemorrhagic encephalitis due to arsphenamine.

Toxic Hepatitis Due to Arsphenamine.—Wile and Sams⁴⁹ provide the most recent thorough review of this important topic on the basis of 65 personally observed patients. Jaundice due to treatment developed in 1.3 per cent of the patients treated in their clinic. All the arsenical drugs employed, including tryparsamide, were about equally responsible. Dosage was not a factor. The hepatitis occurred from one to one hundred and thirty-nine days after the last treatment, with early (fifth day) and late (about the ninety-fifth day) peaks. The cause of the reaction is not clear. The authors do not subscribe to the French view that it is due to syphilis of the liver (hepatorecurrence) and state that they feel that there is inadequate chemical evidence to justify the theory that the toxic action is due to retention of arsphenamine in the liver. Chemical studies supporting this theory are lacking. On the whole, the authors favor the theory that the disease is related in some manner to epidemic infectious jaundice. This is supported by the clinical course, which is indistinguishable from so-called acute catarrhal jaundice, and by epidemiologic data. However, necropsy observations in the fatal cases of acute yellow atrophy following the use of arsphenamine indicate that the icterus results from severe intoxication and destruction of the hepatic substance analogous to other forms of poisoning which lead to acute yellow atrophy. Until more accurate means are at hand for the determination of susceptibility to arsphenamine and of hepatic function and until the drug is modified to make it less hepatotoxic, jaundice

46. Plass, E. D., and Woods, E. B.: Hemorrhagic Encephalitis (Neoarsphenamine) in Obstetric Patients, *Am. J. Obst. & Gynec.* **29**:509, 1935.

47. Chetverikov, N. S., and Kavyrshin, A. Y.: Symptoms of Lesions of Spinal Cord Following Neoarsphenamine Injections, *Klin. med.* **12**:1374, 1934.

48. Osterberg, A. E., and Kernohan, J. W.: Presence of Arsenic in the Brain and Its Relation to Pericapillary Hemorrhages or So-Called Acute Hemorrhagic Encephalitis, *Am. J. Clin. Path.* **4**:362, 1934.

49. Wile, U. J., and Sams, W. M.: A Study of Jaundice in Syphilis: Its Relation to Therapy, *Am. J. M. Sc.* **187**:297, 1934.

due to arsphenamine will continue to be among the severe complications of the modern treatment of syphilis.

Baldrige⁵⁰ offers the disquieting suggestion that antisyphilitic treatment may be responsible for cirrhosis of the liver. He reports the cases of 12 patients with portal cirrhosis, none of whom had had either syphilis of the liver or postarsphenamine jaundice, but all of whom had received antisyphilitic treatment (in at least 10 instances including an arsphenamine) usually within from six to eight months preceding the development of the hepatic symptoms. In no instance was clinical evidence of disease of the liver found before the antisyphilitic treatment was begun. In 3 of 4 patients who came to necropsy the cirrhosis was of the toxic type (i. e., the result of a previous acute yellow atrophy), an observation which seems strange in view of the author's definite statement that "in no case was there a history of post-arsphenamine jaundice, and no symptom which would suggest a non-fatal acute yellow atrophy of the liver was observed while the patients were under treatment." Although Baldrige's observations are foreign to the experience of most observers, his remarks should prompt additional study of this important question.

Postarsphenamine Dermatitis.—Shaffer⁵¹ summarizes current opinion and practice with regard to the treatment of the distressing complication, postarsphenamine dermatitis. He still holds that sodium thiosulphate is of some value, especially if used early, in spite of the fact that no experimental evidence supports this view and that the clinical evidence is far from convincing. He reviews the literature on the use of liver extract and of calcium salts, both of which have been employed empirically by various observers and with varying success. Of most value, he says, is the intravenous administration of dextrose (50 cc. of a 50 per cent solution daily for from three to five days). The chief tangible rationale of this method of treatment lies in the hypothesis that the glycogenic function of the liver is disturbed during postarsphenamine dermatitis (which hypothesis, incidentally, has not been proved), in the supposed influence of the dehydrating effect of dextrose in promoting the transfer of toxic substances from tissue to blood and hence to excretory organs (also not proved for arsphenamine or its split products) and in the fact that dextrose added to solutions of arsphenamine before their administration lowers their toxicity. Other less tangible hypotheses are also offered in support of the idea. The clinical impressions of the author and of several discussers of his paper were all favorable to this method of treatment, which, as may be seen, still rests on an unsatisfactory empirical basis. Too little is known of the exact mechanism

50. Baldrige, C. W.: The Relationship Between Antisyphilitic Treatment and Toxic Cirrhosis, *Am. J. M. Sc.* **188**:685, 1934.

51. Shaffer, L. W.: Treatment of Postarsphenamine Dermatitis, *Arch. Dermat. & Syph.* **29**:173 (Feb.) 1934.

of the production of arsphenamine dermatitis to permit the development of an entirely rational treatment.

The Determination of Arsphenamine Sensitivity by Patch and Intravenous Testing.—Some varieties of postarsphenamine dermatitis are expressions of permanent sensitization, while others are not; and in the former group the sensitization is sometimes drug-specific rather than group-specific. These facts make it important to determine in certain patients whether sensitization to a specific member of the arsphenamine series persists, preventing the further use of any of these drugs. Jordan and Osborne⁵² take the same position as Robinson,⁵³ namely, that the patch test is not a reliable guide to further treatment with arsphenamine following recovery from arsphenamine dermatitis and that the only safe method of determining whether more arsphenamine can be tolerated by such patients is by the intravenous administration of minute, gradually ascending doses of the drug in question.

Cannon and Karelitz,⁵⁴ in an article that is longer than the relative importance of the subject justifies, conclude that the intradermal test for arsphenamine sensitivity is, like the patch test, unsatisfactory since it is often negative in patients known to be sensitive and sometimes positive in patients known not to be sensitive.

The conclusions stated in these three papers are in direct contradiction to the work of Schoch,⁵⁵ who says that the patch test is sufficiently reliable to be employed as a guide in treatment. My personal experience leads me to join the majority in their opinion that the patch and intradermal tests are of no practical value.

The Treatment of Heavy Metal Poisoning.—In view of the apparently complete inefficacy of sodium thiosulphate and of calcium preparations in the treatment of arsphenamine dermatitis and jaundice (most recently reported on by Keim⁵⁶), the success reported by Rosenthal⁵⁷ in

52. Jordan, J. W., and Osborne, E. D.: Observations on Arsphenamine Dermatitis, with Especial Reference to the Reliability of the Patch Test, New York State J. Med. **35**:210, 1935.

53. Robinson, H. M.: Patch Tests in the Determination of Arsphenamine Sensitivity, South. M. J. **27**:845, 1934.

54. Cannon, A. B., and Karelitz, M. B.: Intradermal Tests in Relation to Arsphenamine Dermatitis, Arch. Dermat. & Syph. **29**:485 (April) 1934.

55. Schoch, A. G.: Arsphenamine Dermatitis: Attempted Sensitization to Neoarsphenamine and Further Observations on the Patch Test, Arch. Dermat. & Syph. **30**:672 (Nov.) 1934.

56. Keim, H. L.: "Erythema of the Ninth Day" Following Administration of Arsphenamine: Preliminary Report, Arch. Dermat. & Syph. **31**:291 (March) 1935.

57. Rosenthal, S. M.: Experimental Studies on Acute Mercurial Poisoning, Pub. Health Rep. **48**:1543, 1933; An Antidote for Acute Mercury Poisoning, J. A. M. A. **102**:1273 (April 21) 1934.

the treatment of mercury poisoning in experimental animals and man by means of sodium formaldehyde sulfoxylate is of interest. Unfortunately, Brown and Kolmer⁵⁸ were unable to confirm Rosenthal's results in animals. In order to save rabbits poisoned with mercury the antidote had to be administered within an hour after the mercury had been administered.

THE USE OF MALARIA IN THE TREATMENT OF DRUG-RESISTANT SYPHILIS

In a very brief paper Dennie and McBride⁵⁹ point out the value of malaria therapy in patients with either early or late syphilis whose lesions fail to heal under the ordinary drug therapy. They express the belief that the etiologic factor in such cases is not the inefficacy of the drugs employed but the failure of the defense mechanism of the body. The effect of malaria is to reactivate the defense mechanism and to enhance the value of subsequent treatment. I have had identical experiences, hold identical beliefs and regret that the authors did not present these important facts in greater detail.

CEREBROSPINAL FLUID

Headaches Following Lumbar Puncture.—In one paper of an interesting series on intracranial hydrodynamics, Masserman⁶⁰ proposes a relatively new explanation for severe postpuncture headache. He says that this reaction, appearing two or more hours after puncture, could not be due to intracranial hypotension, since the pressure of the cerebrospinal fluid following the removal of even large amounts of fluid returned to its original level within one or two hours and then mounted. Furthermore, postpuncture headache almost invariably occurred when the development of subarachnoid hypotension was prevented by the immediate reinjection of the fluid removed. It is therefore highly probable that the symptoms are due not only to a simple mechanical alteration in the subarachnoid hydrostatics but also to the congestion and edema of the central nervous system resulting from severe disturbances in its fluid balance. Leakage through the puncture wound in the dura plays little if any part in the causation of headache, according to Masserman. He

58. Brown, H., and Kolmer, J. A.: Sodium Formaldehyde Sulfoxylate in Experimental Acute Mercury Poisoning, *J. Pharmacol. & Exper. Therap.* **52**:462, 1934.

59. Dennie, C. C., and McBride, W. L.: Treatment of Resistant Somatic Syphilis, *Arch. Dermat. & Syph.* **30**:1 (July) 1934.

60. Masserman, J. H.: Intracranial Hydrodynamics: III. Central Nervous System Shock and Edema Following Rapid Fluid Decompression of Ventriculo-Subarachnoid Spaces, *J. Nerv. & Ment. Dis.* **80**:138, 1934.

is of the opinion that headache may be minimized by withdrawing the spinal fluid very slowly and that if it does develop it is best treated by measures calculated to relieve the shock and edema of the central nervous system (i. e., rest and the intravenous administration of dextrose, 250 cc. of a 20 per cent solution). The article is also valuable for a bibliography of 109 references.

Other Complications of Lumbar Puncture.—Reynolds and Wilson⁶¹ report 3 interesting cases in which diagnostic lumbar puncture (the cerebrospinal fluid was normal in 2 cases and the condition was not mentioned in the third case) was followed in from six to twelve hours by headache, stiffness of the neck, stupor, delirium and fever. Repeated examination of the spinal fluid revealed sterile, cloudy fluid, with cell counts of 2,900, 3,780, and 17,670, respectively (from 85 to 95 per cent of the cells were polymorphonuclears), and there was prompt spontaneous recovery.

Among the little stressed complications of lumbar puncture is injury to the vertebrae. The report by Pease⁶² is of special interest to me because of my experience with a patient in whom severe and disabling osteomyelitis of the third lumbar vertebra developed following lumbar puncture. Pease, prompted by the complaint of pain in the lower part of the back in many patients after lumbar puncture, observed in 12 cases thinning of the intervertebral disks and definite sclerosis of the vertebral bodies. This untoward result may occur if the needle is introduced too far and penetrates the intervertebral disk.

The Blood Spinal Fluid Barrier.—Masserman,⁶³ utilizing sodium bromide in 28 patients with dementia paralytica, confirms the results of Malamud and others that the permeability of the blood-spinal fluid barrier in this disease is significantly lower than in schizophrenic and in normal persons. The significance of these observations is not clear, either as to the etiology of neurosyphilis associated with dementia paralytica or as to its treatment, since in successfully treated patients it has been shown that the permeability of the barrier increases to or above normal. Considering the inefficacy of chemotherapeutic treatment (except with tryparsamide) in dementia paralytica, these results are the reverse of what would be expected.

61. Reynolds, K. E., and Wilson, G.: Aseptic Meningitis Following Diagnostic Lumbar Puncture, *J. A. M. A.* **102**:1460 (May 5) 1934.

62. Pease, C. N.: Injuries to Vertebrae and Intervertebral Disks Following Lumbar Puncture, *Am. J. Dis. Child.* **49**:849 (April) 1935.

63. Masserman, J. H.: Blood-Cerebrospinal Fluid Barrier, with Especial Reference to Changes in General Paralysis and in Dementia Praecox, *Psychiatric Quart.* **9**:48, 1935.

TREATMENT IN EARLY SYPHILIS

The most important study of recent years dealing with the results of treatment of early syphilis is that of the Cooperative Clinical Group.⁶⁴ Five large clinics for syphilitic patients (the universities of Pennsylvania, Michigan, Western Reserve and Johns Hopkins and the Mayo Clinic) pooled their material and with the aid of the United States Public Health Service subjected it to critical statistical analysis. The detailed reports were published in *Venereal Disease Information* during 1931 and 1932. More readable summaries which omit the statistical details are provided in later important papers. The following summary is in part a direct quotation:⁶⁵

The maximum frequency of relapse in early syphilis under observation and treatment 6 months or longer is 19.7%. . . . The incidence of mucocutaneous relapse is lowest in those patients who have had a full secondary reaction to the disease. Patients who begin treatment in the seropositive primary stage have the highest incidence of mucocutaneous relapse. Nonetheless, no advantage appears on other grounds in permitting a seropositive primary case to go on to secondaries. The seropositive primary case must be treated with exceptional thoroughness. Relapse decreases in frequency with an increasing number of arsphenamine injections except in the case of cardiovascular and asymptomatic neurosyphilis. Satisfactory ("curative") treatment results are obtained in cases observed 2 years or longer (up to 20 years) in 52.7% of cases without respect to amounts and methods of treatment. Treatment begun in seronegative primary syphilis by a "continuous" system yields 86.4% "satisfactory results." The proportion of "satisfactory results" drops to 64.3% by the same method if the treatment is delayed until the serologic tests become positive. If the patient has developed secondaries, the proportion of "satisfactory results" (2 years and after) again rises to 81.5 % by a continuous system of treatment.

The authors state that the continuous method of treatment far out-ranks other systems (intermittent, intensive and irregular) in the proportion of ultimately satisfactory clinical outcomes. However, disregarding the system of treatment used, the optimum amount of arsphenamine was found to be: for seronegative primary syphilis, from 10 to 19 injections (preferably the higher number); for seropositive primary syphilis, from 25 to 35, and for early secondary syphilis (first year), from 20 to 29. A high scale of dosage is preferable to a low one. Ars-

64. Stokes, J. H.; Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Wile, U. J.; Parran, T., Jr.; Vonderlehr, R. A., and Usilton, L. J.: Standard Treatment Procedure in Early Syphilis: A Résumé of Modern Principles, *J. A. M. A.* **102**: 1267 (April 21) 1934.

65. Stokes, J. H.; Usilton, L. J.; Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Wile, U. J.; Parran, T., Jr., and McMullen, J.: What Treatment in Early Syphilis Accomplishes: I. Relapse and "Curative" Results, *Am. J. M. Sc.* **188**: 660, 1934; II. Optimum Treatment. *ibid.* **188**:669, 1934; III. Comparison of Bruusgaard's Work and the Three- to Twenty-Year Results of the Coöperative Clinical Group, *ibid.* **188**:678, 1934.

phenamine is definitely superior to neoarsphenamine. In deciding when to stop treatment in the ordinary case, an uneventful clinical and serologic course toward recovery is paramount. In such an uneventful course the parole of the patient to observation after two years of adequate treatment is justified. The irreducible margin of failure in the treatment of early syphilis—the proportion of patients not likely to achieve or maintain a satisfactory result with any type of treatment—ranges from 4 to 29 per cent, depending on the method employed, the stage at which treatment is begun, the adequacy of treatment during the first two years of the infection and other considerations discussed in previous papers.

In comparing the results in the treated Cooperative Clinical Group patients with Bruusgaard's results in untreated patients, it was found that clinical evidence of neurosyphilis developed from two to four times as frequently in untreated as in treated patients and that late cutaneous and osseous lesions are from seventeen to twenty-six times as frequent in untreated patients. From 63 to 77 per cent of treated patients became free from symptoms and gave a negative Wassermann reaction in an observation period of from three to twenty years, as compared with from 24 to 36 per cent without treatment. After adequate treatment by an effective technic 96 per cent of patients became free from symptoms, with positive or negative reactions of the blood, after from three to ten years, while when no treatment was given only 61 per cent became symptom-free. While the relative benignity of many aspects of untreated syphilis is conceded, the results fully justify adequate and systematic modern treatment for early syphilis.

Massive Arsenical Treatment of Early Syphilis.—Chargin, Leifer and Hyman⁶⁶ have restudied the effect of massive doses of arsphenamine on early syphilis. They report on 25 patients, each of whom was given a total dose of from 2.4 to 5 Gm. of neoarsphenamine in from four to six days, the average daily dose being 1 Gm. No further treatment was given. The original feature of the method was the administration of the drug by slow intravenous drip, each daily injection being given in from approximately 1,000 to 1,500 cc. of a 5 per cent solution of dextrose over a period of from six to twelve hours. The theory was to reduce toxicity and to provide a massive sterilizing dose of the drug. The former aim was hardly accomplished, since in eight patients (32 per cent) polyneuritis developed and was severe in 2 instances. However, no other serious complications occurred. Nine of the 25 patients

66. Chargin, L.; Leifer, W., and Hyman, H. T.: Studies of Velocity and the Response to Intravenous Injections: V. The Application of the Intravenous Drip Method to Chemotherapy, as Illustrated by Massive Doses of Arsphenamine in the Treatment of Early Syphilis, J. A. M. A. **104**:878 (March 16) 1935.

were followed for more than sixteen weeks (for total periods ranging from six to twelve months). In all these the serologic reactions became negative, and no clinical relapses were observed.

I am less enthusiastic than the authors about the adoption of this method on a large scale because of (1) the high incidence of polyneuritis as a complication of treatment; (2) the almost invariable early or late clinical relapses observed after large single (or multiple) doses of arsphenamine given in the first few years after its introduction in 1909 and 1910; (3) the comparatively complete inefficacy on all counts of the intensive (Pollitzer) system of treatment, as shown by the careful studies of the Cooperative Clinical Group; (4) the inadequate period of observation of the patients so far treated; (5) the lack of demonstration that the intravenous drip method of administering 1 Gm. of, for example, arsphenamine is superior in therapeutic effect to the administration of the same amount in a small volume of fluid and in a short period of time, and (6) the absence of evidence of the harmlessness of this method of treatment in experimental animals.

GLANDULAR TRANSFER AS EVIDENCE OF CURE OF SYPHILIS

Lunsford and Day⁶⁷ have performed the largest recorded series of inoculations of rabbits with the inguinal glands of untreated and treated syphilitic patients. Infection was transmitted to animals successfully with material from the following patients: 8 patients with untreated primary syphilis, 100 per cent; 29 patients with late syphilis, no previous treatment, 38 per cent; 38 patients with late syphilis, previously treated but not for two years, 31.5 per cent; 19 patients with late syphilis under active treatment at the time of the test, none; 6 patients with dementia paralytica, no previous treatment, none. The authors lay great stress on the fact that in 3 of the patients previously treated intensively treatment had been started at the time of primary or secondary syphilis and had consisted of from forty-one to one hundred and twenty-eight injections of neoarsphenamine plus appropriate amounts of a bismuth and/or mercury preparation. These patients had been dismissed as "cured" on the basis of negative serologic tests, but glandular transfer was nevertheless effected from three to five years later. However, since the Wassermann reaction of the blood in all these patients was positive at the time of the transfer and since nothing is said about clinical evidences of reinfection or relapse, the case reports are robbed of much of their meaning. The conclusion to be drawn from these experiments is that glandular transfer from human beings to animals is of no value as a criterion of cure (as is transfer from rabbit to rabbit), since

67. Lunsford, C. J., and Day, P. W.: Transference of Inguinal Glands in Human Syphilis, *J. A. M. A.* **102**:448 (Feb. 10) 1934.

the test gives negative results in such a high proportion of patients with previously untreated and active late syphilis.

TREATMENT OF BENIGN LATE SYPHILIS

Adding to the completeness of studies of the results of treatment of various types of syphilitic infection, Wasserman and Goodman⁶⁸ recount the clinical outcome of treatment in 250 patients with benign late (i. e., mucocutaneous and osseous) syphilis. Their important conclusions are as follows: The outcome of treatment must be measured in clinical rather than serologic terms; a persistently positive Wassermann reaction in a case of benign late syphilis does not imply a gloomy clinical prognosis, nor does reversal of the reaction guarantee against subsequent clinical relapse; the incidence of clinical relapse is directly related to the amount of treatment given (31 per cent with one course of treatment or less, 5 per cent with four courses or more); the character of the relapse is particularly likely to be of the same allergic gummatous type as the original lesion, and the optimum amount of treatment in such cases appears to be from five to seven courses each of an arsphenamine and a heavy metal given continuously over an average period of from eighteen to twenty-four months.

LATENT SYPHILIS

Carriers of Syphilis.—The question as to the potential infectiousness of a patient with late syphilis is of great importance, both from the personal and from the public health standpoint. Since Eberson and Engman reported in 1921 that in 2 of 11 men with late syphilis the semen was infectious for rabbits, the subject has not received the attention it deserves. Kertész has stated in recent years that by means of inoculation of semen into the vitreous of the eye of rabbits he is able to produce what he calls syphilitic keratitis with a high degree of frequency. Unfortunately, proof that this keratitis is syphilitic is completely lacking. The paper by Greenbaum, Katz and Rule⁶⁹ is therefore particularly timely. They inoculated rabbits intratesticularly with the semen of 7 patients with "acute" (early?) syphilis, of 17 with various forms of late or latent syphilis and of 1 with congenital syphilis. All the inoculations gave negative results, as confirmed by transplants of lymph nodes from the original animals to fresh rabbits. Unfortunately,

68. Wasserman, H., and Goodman, M. J.: The Results of Treatment in Late Mucocutaneous and Osseous (Benign Late) Syphilis, *Am. J. Syph. & Neurol.* **18**:458, 1934

69. Greenbaum, S.; Katz, S., and Rule, A.: Syphilis and Marriage: An Inquiry into the Infectiousness of Semen of Patients Under Treatment for Syphilis, *Am. J. Syph. & Neurol.* **19**:210, 1935.

the study is less important than it might have been, since all the patients had been under energetic treatment for syphilis for some weeks or months preceding the test. What is really needed are similar experiments utilizing patients who have never had treatment or at least have not been treated for several years preceding the test.

Blood Transfusion and Syphilis.—This subject has recently been reviewed, and cases have been added by Jones, Rathmell and Wagner⁷⁰ (4 personal cases) and by Morgan⁷¹ (1 case). The most remarkable feature of these two communications is that in spite of the known frequency of this disastrous occurrence (I have definite knowledge of 7 instances) a thorough review of the literature reveals the reports of only about 20 recorded cases. In the majority of reported instances the donor had an early stage of the disease. Not a single incontestable case of syphilis due to blood transfusion has been reported in which the disease was transmitted by blood from a donor with latent or chronic syphilis uninfluenced by pregnancy (Morgan's statement, though I have recently observed such a case).

On the whole, it seems safer to agree with Jones, Rathmell and Wagner, who conclude that all syphilitic patients are potential transmitters, and to throw the most rigid safeguards around the procedure of transfusion. These should include (1) a written, not verbal, report of a serologic test of the donor's blood carried out on the day that the transfusion is to be given, (2) physical examination of the donor and (3) the resort to an "emergency" transfusion without these precautions only when immediate action is demanded in order to save a life.

CONGENITAL SYPHILIS

Syphilis and Pregnancy.—The outcome of 943 pregnancies in syphilitic women is reported by McKelvey and Turner⁷² in a paper which constitutes the most important contribution to this subject that has been made in several years. Detailed data are presented to aid in the evaluation of the Wassermann reaction of blood from the cord (which the authors believe to be of distinct though not of definitive value), of the histologic characteristics of the placenta, of roentgenograms of an infant's long bones and of the results of a follow-up study and pediatric study in determining the presence or absence of syphilis in an infant. It is clearly shown that with adequate treatment (the results being pro-

70. Jones, H. W.; Rathmell, T. K., and Wagner, C.: The Transmission of Syphilis by Blood Transfusion, *Am. J. Syph. & Neurol.* **19**:30, 1935.

71. Morgan, H. J.: Factors Conditioning the Transmission of Syphilis by Blood Transfusion, *Am. J. M. Sc.* **189**:808, 1935.

72. McKelvey, J. L., and Turner, T. B.: Syphilis and Pregnancy, *J. A. M. A.* **102**:503 (Feb. 17) 1934.

portional to the amount of treatment given and the time at which it is begun) congenital syphilis may be prevented (or if established, successfully treated in utero) with almost absolute certainty.

The survey of the Cooperative Clinical Group ⁷³ on this same subject gives a review of the outcome of 607 pregnancies in syphilitic women. The conclusions are practically identical with those of McKelvey and Turner.

McCord's latest paper ⁷⁴ gives the reports of 2,500 additional well studied cases. The outcome of pregnancy with varying amounts of antisyphilitic treatment and the effect of treatment on such factors as the Wassermann reaction of blood from the cord and necropsy and roentgenologic observations on dead infants are presented in a series of illuminating tables.

Eastman and Dippel ⁷⁵ have made an important contribution to the solution of the question: Does treatment of the syphilitic pregnant woman prevent infection of the fetus, or may it also treat a fetus with an already established infection? Although they were unable to demonstrate arsenic in the fetal blood following treatment of the mother with arsphenamine, it was observed in substantial concentration in the meconium. This suggests that whatever the manner (probably not simple diffusion through the placenta) in which arsenic is transmitted from mother to fetus, arsenic is metabolized by the fetus in the usual manner and is available for the treatment of an already established fetal infection.

Experimental Fetal Syphilis.—Attempts to solve experimentally some of the problems of the transmission of syphilis from mother to fetus have been made by Levaditi and his associates,⁷⁶ Nyka ⁷⁷ and

73. Cole, H. N., and others: Syphilis in Pregnancy, Ven. Dis. Inform. **15**:83, 1934.

74. McCord, J. R.: Syphilis and Pregnancy: A Clinical Study of 2,150 Cases, J. A. M. A. **105**:89 (July 13) 1935.

75. Eastman, N. J., and Dippel, A. L.: The Passage of Arsenic Through the Human Placenta Following Arsphenamine Therapy, Bull. Johns Hopkins Hosp. **53**:228, 1933.

76. Levaditi, C.; Hornus, G.; Vaisman, A., and Schoen, R.: Présence du virus syphilitique dans l'ovaire des souris syphilitisées par voie sous-cutanée, Compt. rend. Acad. d. sc. **197**:798, 1933. Levaditi, C.; Schoen, R.; Manin, Y., and Vaisman, A.: Présence de *T. pallidum* dans l'utérus des souris contaminées de syphilis, Compt. rend. Soc. de biol. **114**:687, 1933; Présence de *T. pallidum* dans l'ovaire des souris contaminées de syphilis, Compt. rend. Acad. d. sc. **197**:1364, 1933; Infection treponémique utéro-ovarienne et cycle oestral folliculinique chez la souris blanche, Compt. rend. Soc. de biol. **116**:376, 1934. Levaditi, C.; Vaisman, A.; Schoen, R., and Manin, Y.: Tentatives de transmission héréditaire de l'infection syphilitique inapparente chez la souris blanche, *ibid.* **118**:962, 1935.

77. Nyka, W.: Contribution à l'étude du mécanisme de la transmission de la syphilis de la mère à l'embryon chez la lapine et la souris, Compt. rend. Soc. de biol. **114**:1258, 1933.

Seiffert.⁷⁸ Though the uterus and ovaries of the syphilitic white mouse can be shown (by transfer of organs from a rabbit) regularly to contain virulent spirochetes, this has no apparent effect on the fecundity or on the fetal mortality. In the mouse the placenta seems to be impermeable to the virus, and the young are never infected (Levaditi and his associates). Seiffert confirms this statement as to the mouse, but in rabbits he has apparently demonstrated the virus in some instances in the placenta and, if the placenta was infected, in the young as well. Nyka has tried the artificial experiment of directly inoculating the ovaries of rabbits, breeding them subsequently. He also expresses the belief that following this procedure the fetus may become infected and that, depending on the duration of pregnancy, either "filamentous" or spiral forms of the virus can be demonstrated in the fetal tissues.

While the results of these three studies are inconclusive, this type of investigation merits further pursuit, since the experimental approach is the only one likely to be productive of a solution.

Interstitial Keratitis.—In a paper well supplied with bibliographic references Klauder⁷⁹ discusses the relationship of trauma to interstitial keratitis in syphilis. A general discussion of the relationship of trauma to the localization of syphilitic lesions in man and experimental animals is provided. Occasionally, trauma precedes the development of interstitial keratitis in man, and workmen's compensation boards have usually favored the plaintiff in this connection. Experimental studies in rabbits were inconclusive.

Ambler and Van Cleve⁸⁰ report the results of malarial therapy in 17 patients with interstitial keratitis, in 10 of whom previous chemotherapy had been unsatisfactory. The results were excellent in all, even in the most chronic cases.⁸¹ The authors express the belief that malarial treatment possesses distinct advantages over any other known method of treatment for interstitial keratitis.

Treatment of Interstitial Keratitis with Quinine.—In view of the poor results of antisyphilitic treatment in some cases of interstitial keratitis, Selinger⁸² was moved to try the local application of 2 per cent

78. Seiffert, W.: Experimentelle Untersuchungen über die Infektion mit *S. pallida* durch Kohabitation und durch die Plazenta, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **83**:386, 1934.

79. Klauder, J. V.: Ocular Syphilis: IV. Interstitial Keratitis and Trauma; Clinical, Experimental and Medicolegal Aspects, *Arch. Ophth.* **10**:302 (Sept.) 1933.

80. Ambler, J. V., and Van Cleve, J. V.: Malarial Therapy in Syphilitic Interstitial Keratitis, *J. A. M. A.* **102**:1553 (May 12) 1934.

81. See also Dennie and McBride.⁵⁹

82. Selinger, E.: Local Quinine Therapy in Cases of Interstitial Keratitis and Old Corneal Opacities, *Arch. Ophth.* **13**:829 (May) 1935.

quinine bisulphate ointment. Quinine, he says, not only is bactericidal and astringent but destroys leukocytes and lymphocytes and probably aids in the resorption of abnormal tissue elements, such as newly formed connective tissue in the cornea. He used this treatment on several patients with active interstitial keratitis and on several others without active keratitis but with dense corneal opacities and claims that some improvement was obtained in all.

Articular Changes in Late Congenital Syphilis.—Klauder and Robertson⁸³ review the literature and describe the cases of 63 personally observed congenitally syphilitic patients with symmetrical serous synovitis (Clutton's joints). This is a manifestation of late congenital syphilis, usually involving the knees. The authors describe the clinical course, the age incidence (usually between 8 and 15 years), the absence of changes that are demonstrable in roentgenograms, the pathology, the differential diagnosis, the response to treatment, the incidence as compared to other stigmas of congenital syphilis (17 per cent of 363 patients in their series had Clutton's joints) and the peculiar tendency of this lesion to be associated with interstitial keratitis.

Juvenile Dementia Paralytica.—In a series of twelve interesting, important and well documented articles, eleven of which have appeared, Menninger⁸⁴ reviews in monographic form the entire subject of juvenile dementia paralytica. His conclusions are based on 45 personally observed patients and on 610 cases reported in the literature. The more important of his conclusions that have been published are as follows: In about 1 per cent of all patients with congenital syphilis, juvenile dementia paralytica develops, a lower incidence than in patients with the acquired disease. While dementia paralytica in the acquired form is nearly three and one-half times as frequent in men as in women, the juvenile form has an almost equal incidence in boys and in girls.

83. Klauder, J. V., and Robertson, H. F.: Symmetrical Serous Synovitis (Clutton's Joints), *J. A. M. A.* **103**:236 (July 28) 1934.

84. Menninger, W. C: Juvenile Dementia Paralytica: I. Incidence, Sex and Age of Onset, *Am. J. Syph. & Neurol.* **18**:486, 1934; II. Family History, *Arch. Int. Med.* **55**:626 (April) 1935; III. Developmental History, Including Mental and Physical Growth, Trauma and Convulsions, *J. Nerv. & Ment. Dis.* **81**:489 (May) 1935; IV. Syndrome of the Cranial Nerves and Motor System, *Arch. Neurol. & Psychiat.* **34**:243 (Aug.) 1935; V. Sensory Changes and the Reflexes in Juvenile Paretic Neurosyphilis, *Ann. Int. Med.* **8**:1287 (April) 1935; VI. Physical Complications, Stigmas, and Endocrinopathies, *Am. J. Syph. & Neurol.* **19**:88, 1935; VII. The Descriptive Mental Picture, *Am. J. Psychiat.*, **91**:1413 (May) 1935; VIII. The Psychology of Juvenile Dementia Paralytica, *Psychoanalyt. Rev.*, to be published; IX. Laboratory Findings, *J. Lab. & Clin. Med.* **20**:806 (May) 1935; X. The Clinical Course, Including Prodromal Symptoms, Nature of Onset, Remissions, and Duration, *Am. J. Syph. & Neurol.* **19**:238, 1935; XI. Treatment, *ibid.* **19**:257, 1935; XII. Gross and Microscopic Pathology, *Arch. Path.* **19**:316 (March) 1935.

The average age at onset is 13 years. Few cases occur before the sixth or after the twentieth year of life. Four times as many mothers of patients with juvenile dementia paralytica have neurosyphilis as unselected syphilitic women, and nearly twice as many fathers have neurosyphilis as average syphilitic men. In both parents the type of neurosyphilis, when present, is predominantly that of dementia paralytica. In the siblings of persons who have had juvenile dementia paralytica, neurosyphilis is likewise common. These facts may be accepted equally well as arguments for a neurotropic strain of virus as for a familial predisposition.

Menninger found that 40 per cent of patients with juvenile dementia paralytica were definitely retarded mentally before the onset of symptoms. The type of preceding feeble-mindedness differed in no way from other types of mental deficiency, but Menninger believes it is an indication of syphilis of the brain. In 35 per cent of all his cases, physical development likewise was retarded. This retardation is primarily an arrest of growth and results in a type of infantilism.

Trauma preceded the onset of symptoms in dementia paralytica in 35 of 349 patients. Convulsions, usually typical of the idiopathic grand mal of epilepsy, occurred at some time, often prior to the development of any other symptom, in 17 per cent of the entire series (31 per cent of those in whom adequate data were provided).

The article on treatment is especially well documented, containing 375 references. The results of treatment are disappointing as compared with those for acquired syphilis. Of 144 cases adequately reported, marked improvement occurred in 13.8 per cent, slight improvement in 25.1 per cent and no effect in 61.1 per cent. The therapeutic agents employed included malaria, diathermy, arsphenamine and tryparsamide. The following factors condition the outcome of treatment: Patients who acquire the disease after a period of normal growth respond better than basically feeble-minded subjects; the onset of symptoms during or after puberty offers a better prognosis than an onset prior to that time; the outlook is better the sooner treatment is inaugurated after the onset of symptoms of dementia paralytica; the influence of previous antisyphilitic treatment, of the sex of the patient and of the type of the psychosis does not seem to play any prognostic rôle; malaria, diathermy and tryparsamide have all given better results than the arsphenamines; treatment must be intensive, prolonged and continuous, i. e., without rest periods.

The pathologic picture of juvenile dementia paralytica, while similar in most respects to that in the adult form, shows certain differences. The characteristic macroscopic changes are generalized atrophy, often hypoplastic, of the brain; marked leptomeningitis; frequently hydro-

cephalus, and extensive ependymitis granulosa. In rare cases gummas of the brain may be present. Microscopically, there are generalized round cell infiltration, extensive neuroglial and microglial proliferation, an increase in vascularity with proliferative changes in all the elements of the vessel walls, a reduction of the number of nerve cells in the cortex and binucleated Purkinje cells in the cerebellum. Spirochetes have been demonstrated in the cortex, the basal ganglions and the cerebellum.

Potter⁸⁵ reports the results of treatment in 60 personally observed patients with juvenile dementia paralytica. The arsphenamines were useless. In 27 of 38 patients (the surprisingly high figure of 71 per cent) treated with malaria, tryparsamide or both, further deterioration was prevented. Five patients achieved a complete, and 9 a partial, remission. The period of observation was in most cases from two to five years. The factors influencing prognosis, according to Potter, are essentially those enumerated by Menninger.

The communications of both of these authors are important in pointing out that the malaria-tryparsamide treatment of juvenile dementia paralytica is by no means hopeless and that patients should be given the benefit of a trial.

Use of Acetarsone in Congenital Syphilis.—During the past three years numerous investigators, especially in Germany and in the United States, have studied the effect of acetarsone in congenital syphilis. In most instances the reports have been more glowingly favorable than was warranted by the small number of patients treated and the short period of observation. Pillsbury and Perlman⁸⁶ undertook a study of 73 patients. With commendable caution they conclude that, while the clinical response seemed excellent and the initial serologic response was satisfactory, the method is to be regarded as on trial. They point out that the dosage level is still in dispute, that the desirability of combined therapy with some type of heavy metal has not been determined, that serious reactions are sometimes produced by the drug and that a follow-up of the treated patients for a period of from five to ten years will be essential for a proper evaluation of the method.

Friedman⁸⁷ reports favorably on the use of acetarsone in 5 infants with osseous lesions of congenital syphilis. Baumbach,⁸⁸ with an experi-

85. Potter, H. W.: Treatment of Juvenile General Paresis, *Psychiatric Quart.* **7**:593, 1933.

86. Pillsbury, D. M., and Perlman, H. H.: Treatment of Prenatal Syphilis with Acetarsone (Stovarsol), *Pennsylvania M. J.* **38**:327, 1935.

87. Friedman, C. F.: Acetarsone in the Treatment of Osseous Lesions of Early Congenital Syphilis, *Am. J. Dis. Child.* **48**:548 (Sept.) 1934.

88. Baumbach: Ueber Erfahrungen mit der Spirocicidkur bei Lues Congenita, *Arch. f. Kinderh.* **99**:151, 1933.

ence covering 61 cases, concludes that the best results are obtained when acetarsone is alternated with mercury by inunction. Traisman⁸⁹ has also achieved favorable results in 54 patients. Yampolsky,⁹⁰ on the basis of his experience with 16 children, is disposed to be more cautious. Coppolino⁹¹ and Eckardt⁹² also report on this method of treatment.

In reporting two cases (one fatal) of myelitis and peripheral neuritis following the use of acetarsone in infants, Glaser⁹³ sounds a timely note of warning that caution is necessary.

GASTRIC SYPHILIS

The perennial argument of therapeutic test versus exploratory laparotomy in patients with suspected gastric syphilis is somewhat clarified by Priestley and Walters.⁹⁴ They point out that a delay of several weeks for a therapeutic test is undesirable if there is any possibility that a lesion is malignant. Cases in which medical treatment is justified from the start are (1) those in which the diagnosis of gastric syphilis is practically certain before a therapeutic test is made (a rare circumstance in my opinion) and (2) those in which the gastric lesion is obviously inoperable, whether as a result of syphilis or of a malignant process. Operation before a therapeutic test is made should be carried out (1) in patients with serologic evidence of syphilis and an operable malignant gastric tumor or a nonspecific inflammatory gastric lesion requiring intervention because of obstruction or perforation and (2) in patients with serologic evidence of syphilis associated with a definite gastric lesion the clinical diagnosis of which is indeterminate between malignancy and syphilis (in my personal experience most cases of suspected gastric syphilis fall into one of the two latter categories). With commendable caution the authors call attention to the difficulty of recognizing gastric syphilis even at exploration and suggest that if there is any doubt in the mind of the operator, resection, if feasible, should be performed.

89. Traisman, A. S.: Treatment of Congenital Syphilis with Acetarsone (Stovarsol) by Mouth, *Am. J. Dis. Child.* **46**:1027 (Nov.) 1933.

90. Yampolsky, J.: Acetarsone in the Treatment of Syphilis in Negro Children, *Am. J. Dis. Child.* **48**:81 (July) 1934.

91. Coppolino, J. F.: Acetarsone in the Treatment of Congenital Syphilis: A Comparison with Bismuth Therapy, *Am. J. Dis. Child.* **48**:272 (Aug) 1934.

92. Eckardt, F.: Spirozid bei Lues Congenita (Zur Frage der Dosierung und Indikation sowie Ergebnisse), *Jahrb. f. Kinderh.* **141**:278, 1934.

93. Glaser, J.: Clinical Arsenical Myelitis and Neuritis Due to Acetarsone, *Am. J. Dis. Child.* **48**:134 (July) 1934.

94. Priestley, J. T., and Walters, W.: Indications for Operation in Gastric Syphilis, *Surg., Gynec. & Obst.* **58**:1030, 1934.

Pernicious Anemia Following Resection for Gastric Syphilis.—Singer and Steigman⁹⁵ add another to the 4 previously reported cases of pernicious anemia following partial or complete resection for gastric syphilis. Their article is particularly valuable for a summary and bibliography of 33 other instances in which primary anemia followed total or subtotal gastrectomy or gastro-enterostomy for carcinoma, ulcer or some other condition.

CARDIOVASCULAR SYPHILIS

A reawakening of interest in the subject of cardiovascular syphilis has been evident within the past few years, prompted in all probability by the demonstrations that the early diagnosis of uncomplicated syphilitic aortitis is possible with accuracy in many instances before the development of saccular aneurysm or aortic regurgitation and that properly directed treatment is often successful in alleviating symptoms and prolonging life. In the Billings lecture Conner⁹⁶ provides a timely and valuable discussion of the development of knowledge in the general field of cardiovascular syphilis. Lisa and Chandlee⁹⁷ utilize 6 cases as the basis of their discussion of the comparatively frequent association of syphilitic and rheumatic cardiac disease and point out that the combined active infections carry a much graver prognosis than that of either infection when it occurs alone.

Maynard and his associates⁹⁸ report a careful study of the cardiovascular status of 346 patients with syphilis. They have made an effort to study the life history of syphilitic patients with cardiovascular involvement starting with the chancre and ending at necropsy. In this sense their paper is a preliminary communication, since most of their patients are still living. They join with earlier observers in stating that they feel that the diagnosis of uncomplicated syphilitic aortitis is possible with a high degree of accuracy. Their material is particularly noteworthy for the unusually high incidence of cardiovascular syphilis discovered at routine examination. The patients were divided into five groups, depending on the interval between the date of infection and the time of the cardiovascular study, as follows: up to three, from four to nine, from ten to nineteen, from twenty to twenty-nine and for thirty or more years. The

95. Singer, H. A., and Steigman, F.: *Pernicious Anemia Following Resection for Gastric Syphilis*, *Am. J. Syph. & Neurol.* **18**:444, 1934.

96. Conner, L. A.: *Development of Knowledge Concerning the Rôle of Syphilis in Cardiovascular Disease*, *J. A. M. A.* **102**:575 (Feb. 24) 1934.

97. Lisa, J. R., and Chandlee, G. J.: *The Heart and Great Vessels in Combined Syphilitic and Rheumatic Infection*, *Arch. Int. Med.* **54**:952 (Dec.) 1934.

98. Maynard, E. P., Jr.; Curran, J. A.; Rosen, I. T.; Williamson, C. G., and Lingg, C.: *Cardiovascular Syphilis: Early Diagnosis and Clinical Course of Aortitis in Three Hundred and Forty-Six Cases of Syphilis*, *Arch. Int. Med.* **55**:873 (June) 1935.

incidence of detectable cardiovascular syphilis in these five groups increased progressively as follows: 14, 28, 56, 77 and 88 per cent, respectively. Unfortunately, the authors do not give the exact figures for the number of patients in each group with simple aortitis, aortic regurgitation and saccular aneurysm, respectively. Since the patients were predominantly white (81 per cent) and since these figures as to the incidence of clinically (*not* pathologically) recognizable cardiovascular syphilis are so vastly in excess of those reported by other observers the world over, one wonders if some unconscious selection did not enter into the choice of material. Also contrary to the experience of others, the authors conclude that cardiac failure occurs only in those patients in whom syphilitic involvement has passed beyond the stage of simple aortitis to the development of valvular incompetency, aneurysm or narrowing of the coronary arteries. Their final conclusion is, however, of the utmost importance and deserves special emphasis:

It is our opinion that involvement of the aorta begins soon after the chancre has appeared and that in the past, discovery of the presence of the disease has been delayed by the late development of symptoms referable to the heart and more especially by inadequate methods of examination.

The moral for the physician who treats syphilitic patients is clear.

Syphilitic Involvement of the Coronary Arteries.—Van Muijden and Scherf⁹⁹ divide angina pectoris into 6 categories, which they say can easily be differentiated, occurring (1) in coronary thrombosis or infarct, (2) in coronary stenosis (angina of effort), (3) in aortic insufficiency (usually nocturnal and accompanied by an increase in the blood pressure), (4) in paroxysmal tachycardia, (5) in anemia and (6) in syphilitic involvement of the coronary ostia. In cases belonging in the sixth category anginal attacks may develop with or without exertion, and anxiety attacks without pain may occur. During an attack there is tachycardia but no elevation of the blood pressure, and nitrites provide relief. The prognosis is unfavorable. Snider and Hunter¹⁰⁰ describe the necropsy observations in such a case.

On the basis of 15 patients studied clinically and at necropsy, Pincoffs and Love¹⁰¹ conclude that syphilitic stenosis of the coronary ostia

99. van Muijden, N. H., and Scherf, D.: Ueber ein durch hochgradige luische Verengung der Coronarostien hervorgerufenen Krankheitsbild, Wien. klin. Wchnschr. **47**:746, 1934.

100. Snider, G. A. C., and Hunter, W. C.: Syphilitic Aneurysm of the Left Coronary Artery with Concurrent Aneurysm of the Sinus of Valsalva, Am. J. Path. **10**:757, 1934.

101. Pincoffs, M. C., and Love, W. S.: Observations upon Syphilis of the Heart, Coronary Ostia, and Coronary Arteries: I. With Special Reference to Clinical Picture Produced by Syphilitic Stenosis of Coronary Ostia, Am. J. Syph. & Neurol. **18**:145, 1934; II. With Special Reference to the Myocardial Lesions Noted in Stenosis of the Coronary Ostia, *ibid.* **18**:154, 1934.

is a very common lesion. It is rarely latent; the clinical course after the onset of symptoms is usually brief and characterized by a lack of response to treatment, a high incidence of the occurrence of anginal pain and a marked tendency to terminate by sudden death. The coincidence of these factors in a patient with cardiovascular syphilis constitutes a clinical picture recognizable as syphilitic occlusion of the coronary ostia. The myocardial lesions present in such cases are explainable on the basis of a defective coronary circulation due to obliterative endarteritis of the coronary arterioles. No pathologic evidence justifying a diagnosis of syphilitic myocarditis could be demonstrated.

Thyroidectomy as a Method of Tréatment for Advanced Syphilitic Cardiac Disease.—In the brilliant series of studies of Blumgart, Levine and their associates¹⁰² on the treatment of advanced cardiac decompensation and angina pectoris by total thyroidectomy, syphilitic cardiac disease has been purposely almost completely excluded on the ground that the lesion in such instances is almost surely progressive and amenable only to temporary, if any, improvement. Since in the early phases of this condition this method of treatment was purely experimental, it was justifiable to limit its use to the most favorable type of cases. With the demonstration by Moore, Danglade and Reisinger,¹⁰³ among others, that symptoms may be alleviated and life prolonged by the properly controlled use of antisypilitic treatment, trial of the method of thyroidectomy in selected cases of syphilitic cardiac disease seems desirable. Pratt¹⁰⁴ takes the same point of view and presents cases which suggest the favorable action of the procedure. Only patients for whom other therapeutic measures have failed are at present eligible for the operative procedure.

The Effect of Antisyphilitic Treatment in Prolonging Life in Cases of Cardiovascular Syphilis.—The contentions of Moore, Danglade and Reisinger¹⁰³ that properly conducted antisypilitic treatment in cases of cardiovascular syphilis will materially prolong life have found some support in the monumental study of Grant¹⁰⁵ from the clinic of Sir Thomas Lewis. Included in this report are the cases of 189 patients with syphilitic aortic insufficiency who were followed until death or, if

102. Blumgart, H. L., and others: Total Ablation of Thyroid in Angina Pectoris and Congestive Failure: Summary of Results in Treating Seventy-Five Patients During Last Eighteen Months, *J. A. M. A.* **104**:17 (Jan. 5) 1935.

103. Moore, J. E.; Danglade, J. H., and Reisinger, J. E.: The Treatment of Cardiovascular Syphilis, *Arch. Int. Med.* **49**:879 (June) 1932.

104. Pratt, G. H.: Complete Thyroidectomy in Advanced Heart Disease, with Observations on Its Use in Advanced Arteriosclerosis, Syphilis, and Renal Disease, *Am. J. Surg.* **28**:85, 1935.

105. Grant, R. T.: After Histories for Ten Years of a Thousand Men Suffering from Heart Disease, *Heart* **16**:275, 1933

living, for a minimum period of ten years. Some of these patients had been allowed to go without antisyphilitic treatment, some had received potassium iodide only and some had been given neoarsphenamine, mercury (at intervals) and potassium iodide. The general medical care was the same for all the patients. There appeared to be no advantage in the use of potassium iodide alone, and the outcome in this and that in the untreated groups were so similar that they may be combined. During the period of observation the mortality rate from all causes in these two groups was 66 per cent, the deaths due directly to cardiovascular syphilis constituting 59 per cent. The corresponding figures for the treated patients were, on the contrary, 49 and 33 per cent, a very material reduction. Grant discusses many collateral factors affecting prognosis in this and other types of cardiac disease.

NEUROSYPHILIS

An interesting symposium on neurosyphilis is presented by Moore, Merritt and Solomon.¹⁰⁶ The subject of acute syphilitic meningitis is covered in monographic fashion in a later publication by Merritt and Moore,¹⁰⁷ on the basis of 80 patients studied by them in Boston hospitals. They provide a complete discussion of the incidence relation to treatment, clinical type, course, serology, pathology, prognosis and treatment, giving a fairly complete bibliography of 66 titles.

The most interesting features of the symposium are those relating to the results of treatment. The authors state that in cases of acute syphilitic meningitis there is a ready response to antisyphilitic drugs and that if treatment is prolonged the ultimate prognosis is good. In cases of dementia paralytica complete arrest and even cure may often be attained by appropriate treatment. Solomon's results with malaria were definitely superior to those obtained with diathermy.

Goodman and Moore¹⁰⁸ have studied the important practical question of the relationship of persistent abnormality of the spinal fluid to the ultimate clinical outcome in treated patients with neurosyphilis. If treatment was given for two or more years, subsequent progression or relapse occurred in 12.5 per cent of the patients who gave persistently positive Wassermann reactions of the spinal fluid as compared with 4.8 per cent

106. Symposium on Neurosyphilis: I. Moore, M.: Acute Syphilitic Meningitis, *J. Nerv. & Ment. Dis.* **80**:320, 1934. II. Merritt, H. H.: Syphilis of the Spinal Cord, *ibid.* **80**:322, 1934. III. Solomon, H. C.: Treatment of Parietic Neurosyphilis, *ibid.* **80**:323, 1934; IV. Solomon, H. C.: Recapitulation, *ibid.* **80**:324, 1934.

107. Merritt, H. H., and Moore, M.: Acute Syphilitic Meningitis, *Medicine* **14**:119, 1935.

108. Goodman, M. J., and Moore, J. E.: Persistent Abnormalities (Wassermann-Fastness) of the Spinal Fluid in Treated Neurosyphilis: Their Prognostic Import, *Arch. Int. Med.* **55**:826 (May) 1935.

of those whose reactions were reversed. They conclude that while there is a slightly more definite relationship between the clinical outcome and the response of the spinal fluid in neurosyphilis than exists between reversal and persistent positivity of the Wassermann reaction of the blood in various forms of late syphilis not involving the nervous system, nevertheless, a persistent abnormality of the cerebrospinal fluid does not indicate the inevitability of subsequent progression or relapse, and the rate or completeness of reversal of the abnormalities of the fluid cannot be used as the sole guide to the optimum duration of treatment in neurosyphilis. Dattner¹⁰⁹ has arrived at essentially similar conclusions.

Involvement of the Eighth Nerve.—Ciocco and Weinstein¹¹⁰ have brought some clarity out of the confused subject of nerve deafness in syphilis, and their study is particularly important because it is the first report in which the audiometer has been used in a detailed study of the problem. Two hundred and eighty-six patients with syphilis were studied, special attention being given to the effects of treatment on hearing. All patients with infection of the middle ear or of deafness antedating the acquisition of syphilis were excluded. Shortened bone conduction in the presence of good hearing was not observed except when the capability of hearing high tones had been lost. Vestibular function was disturbed in half the patients with marked impairment of hearing but was diminished in about 33 per cent of the patients with normal hearing. Involvement of the eighth nerve in acquired syphilis, but not in congenital syphilis, was usually associated with neurosyphilis; but the authors state that a diagnosis of neurosyphilis based solely on an impaired function of the eighth nerve is not justified. There is no evidence that antisyphilitic treatment damages the eighth nerve. With the exception of deafness associated with early meningeal neurosyphilis, treatment is without effect in improving the hearing. The exact site of the lesion in nerve deafness, either in acquired or congenital syphilis, is unknown.

Subdural Treatment of Neurosyphilis.—Bonorino Udaondo and his associates¹¹¹ have experimented with the intraspinal injection of a bismuth compound (bismuth carbonate) in the treatment of various types of neurosyphilis. The drug was tolerated in a dosage of from 0.015 to 0.12 Gm. per injection without untoward results. They report that it is

109. Dattner, B.: Ueber die prognostische Bedeutung der Wassermann-Reaktion bei Neurolues, *Jahrb. f. Psychiat. u. Neurol.* **48**:112, 1932.

110. Ciocco, A., and Weinstein, A.: Involvement of the Eighth Nerve in Syphilis with Special Reference to the Results of Treatment, *Am. J. M. Sc.* **187**:100, 1934.

111. Bonorino Udaondo, C.; Pereyra Kafer, J., and Zunino, H.: Intraspinal Bismuth Therapy, *Prensa méd. argent.* **22**:509, 1935.

as yet too early to measure the clinical improvement. However, there is no reason to believe that the intraspinal administration of bismuth will exercise any effect other than that produced by the subdural injection of other substances, and the weight of American opinion is that this effect is entirely nonspecific.

Treatment of Atrophy of the Optic Nerve.—The present unsatisfactory state of the treatment of primary atrophy of the optic nerve due to syphilis is exemplified by the three papers of Schiff-Wertheimer,¹¹² Gasteiger¹¹³ and Magitot.¹¹⁴ Schiff-Wertheimer believes that some patients are benefited and that arrest of the process is obtained either by subdural or by malarial therapy if treatment is begun at a sufficiently early stage. Gasteiger, on the other hand, is of the opinion not only that malaria is of no benefit but that its use is contraindicated because it occasionally causes a rapid reduction in the visual acuity. Magitot offers the interesting suggestion that syphilitic atrophy of the optic nerve (as well as other forms of primary or retrobulbar atrophy and of diffuse chorioretinitis) should be treated by sympathectomy of the nerve plexus surrounding the common carotid artery. The artery is decorticated for a distance of about 2 cm. up to the bulb of the internal carotid artery, and the carotid ganglion is removed. The two sides are operated on with a supervening interval of from ten to twenty-five days. The physiologic effect produced is a rise in the blood pressure in the peripheral portion of the circulatory system (in 25 per cent of patients), but more particularly there is an increase (permanent?) in the pressure in the retinal arteries and in the entire cerebral circulation, thus improving the blood supply to the diseased area. Magitot reports the cases of 3 patients with primary atrophy of the optic nerve due to syphilis. In the first vision increased from perception of movements of the hands to 1/25; in the second, from complete blindness to perception of light in the left eye and from 1/20 to 1/10 in the right eye, and in the third, from 1/10 (only the left eye affected?) to 4/10. The visual fields were enlarged in all cases. The exact duration of the improvement is not stated but does not exceed four months. In view of the gravity of primary atrophy of the optic nerve due to syphilis, this novel scheme of treatment is perhaps worthy of further trial.

112. Schiff-Wertheimer: Pathogénie et traitement de l'atrophie optique tabétique, Bull. Soc. d'opht. de Paris, no. 8, November 1932, p. 1.

113. Gasteiger, H.: Zur Malariatherapie der tabischen Sehnervenatrophie, Arch. f. Augenh. **108**:471, 1934.

114. Magitot, A.: La sympathectomie carotidienne comme thérapeutique de certaines affections dégénératives du nerf optique et de la rétine, Bull. Acad. de méd., Paris **111**:816, 1934.

Acetarzone in the Treatment of Neurosyphilis.—Griggs and Schamberg¹¹⁵ gave sodium acetarzone intravenously in a weekly dose of 1 Gm. and a total dose of from 8 to 20 Gm. to 17 patients with neurosyphilis. There were subjective improvement in the majority of instances, a noticeable tonic effect similar to that of tryparsamide, some serologic improvement in several cases and one instance of dimness of vision following the administration of the drug. The authors believe the method to be worthy of further trial.

Spiegel¹¹⁶ has treated 25 patients by approximately the same method, giving the drug continuously at weekly or biweekly intervals, however, over a much longer period of time. He also is encouraged by the favorable results obtained.

Use of Tryparsamide in Treatment of Neurosyphilis.—Although the favorable effect of tryparsamide on neurosyphilis has been recognized since 1923, most of the available reports in the literature deal with early rather than late results; and interest in this powerful therapeutic agent has been less than that accorded to the more spectacular fever therapy with malaria and other agents. The survey of 81 patients with dementia paralytica treated with tryparsamide by Solomon and Epstein¹¹⁷ between 1923 and 1930 and restudied in 1933 is therefore of particular value. In 42 per cent a clinical "arrest" (i. e., complete remission) was obtained, in 29 per cent the condition remained stationary and in 28 per cent no improvement was noted. While 14 of the 81 patients died during the period of observation, death was due to unarrested dementia paralytica in only 5, and the average duration of life was greatly prolonged in the living members of the series. The cerebrospinal fluid became normal in 37 per cent and was much improved in 16 per cent, moderately improved in 10 per cent and unimproved in 36 per cent. The period elapsing from the start of treatment to the time at which the spinal fluid became normal varied from one to nine years, and the number of injections of tryparsamide necessary to produce the same result varied from twenty to two hundred and thirty. No significant difference in results was found in patients receiving tryparsamide alone and those receiving other types of antisyphilitic treatment in addition to tryparsamide (except fever therapy). Seventeen patients of the series who did not respond satisfactorily to tryparsamide were subsequently given fever therapy with strikingly beneficial results. A comparison

115. Griggs, L. H., and Schamberg, J. F.: Acetarzone in the Treatment of Neurosyphilis, *Arch. Dermat. & Syph.* **29**:645 (May) 1934.

116. Spiegel, L.: Treatment of Neurosyphilis with Acetarzone (Stovarsol) Given Intravenously, *Am. J. Syph. & Neurol.* **18**:56, 1934.

117. Solomon, H. C., and Epstein, S. H.: Dementia Paralytica: Results of Treatment with Tryparsamide, *Arch. Neurol. & Psychiat.* **33**:1216 (June) 1935.

of these results with those obtained from treatment with malaria in 152 of the author's patients ¹¹⁸ showed no significant differences.

In my opinion, the ideal method of treatment of patients with dementia paralytica is first fever therapy, preferably malaria, followed by treatment with tryparsamide. It is distinctly encouraging to know that when malarial therapy is impracticable (as in patients in poor physical condition or, for reasons of immunity, in Negroes) a weapon of attack as powerful as tryparsamide is available.

Effect of Tryparsamide on the Eye.—In a paper based on the observation of too small a number of cases to be of value, Mayer and Smith ¹¹⁹ arrive at a conclusion diametrically opposite to that of most previous observers and state that tryparsamide does not exert an untoward effect on previously normal eyes. In a more adequate study, Lazar's ¹²⁰ opinion is more in harmony with that of others. He concludes that experimentally there are no changes in the eye, optic nerve, chiasm or brain of lower animals or man which can be definitely attributed to the effects of tryparsamide. Nevertheless, a definite loss of vision immediately after the use of the drug leaves no doubt as to its toxic effect. Serious and even permanent visual damage may result even if the visual apparatus was previously normal, and the drug should not be administered to patients with preexisting atrophy of the optic nerve. The visual fields should be examined as a routine before the use of the drug is started, and this examination should be repeated when subjective visual difficulty becomes apparent or after from three to six injections have been given.

FEVER THERAPY

With the introduction of a series of new physical methods of producing artificial fever, interest in the subject continues. The Council on Physical Therapy of the American Medical Association ¹²¹ sounds a timely note of warning, as follows:

The best method for administering artificial fever induced by physical agents . . . is not firmly established. . . . This method should be used only in hospitals, surrounded with the safeguards commonly employed in a major surgical operation, and under the direction of skilled physicians.

118. Solomon, H. C., and Epstein, S. H.: Dementia Paralytica: Results of Treatment with Malaria in Association with Other Forms of Therapy, *Arch. Neurol. & Psychiat.* **33**:1008 (May) 1935.

119. Mayer, L. L., and Smith, R. D.: Ocular Manifestations of Tryparsamide Treatment of Syphilis, *Illinois M. J.* **65**:258, 1934.

120. Lazar, N. K.: Effect of Tryparsamide on the Eye: An Experimental and Clinical Study and Report of Case, *Arch. Ophth.* **11**:240 (Feb.) 1934.

121. Hyperpyrexia Produced by Physical Agents, Report of Council on Physical Therapy, *J. A. M. A.* **103**:1308 (Oct. 27) 1934.

Bierman and Fishberg¹²² summarize the physiologic changes which occur during this method of treatment. The velocity of the flow of blood is markedly accelerated, the pulse rate rises an average of 8.5 beats per minute for each degree Fahrenheit of elevation of temperature, the systolic blood pressure rises slightly and then falls slightly, and the diastolic pressure falls markedly. Sweating is profuse, but if fluids are freely given, the volume and viscosity of the blood remain unchanged. The respiratory rate rises, and periods of apnea occur. There is first leukopenia and later leukocytosis, due largely to the appearance of young neutrophils and immature forms of leukocytes. There are marked alkalosis and excessive excretion of chlorides (by ultrafiltration) and of lactic acid (by concentration) in the perspiration. The level of chlorides in the blood, urine and gastric juice is lowered. The titer of the complement-fixing antibodies of the blood in animals immunized against various bacteria falls temporarily.

Bishop, Lehman and Warren¹²³ compare the results of fever therapy utilizing diathermy, radiothermy and radiant energy (infra-red rays) and express the belief that the clinical effect and results are the same. The use of radiant energy seems, however, to be the most convenient and economical of the three methods.

Mortimer and Osborne¹²⁴ see no advantage in the short wave diathermy apparatus over conventional diathermy and express their doubt as to the claims that there is specific bactericidal action of these high frequency currents.

Epstein and Cohen¹²⁵ review the literature and report the results of fever treatment in 33 patients with early syphilis. In 94 per cent of the patients spirochetes disappeared from open lesions following treatment with hyperpyrexia alone. Lesions healed, but in 3 patients prompt clinical recurrences developed after the cessation of treatment. Reversal of the serologic reactions was not obtained in any case. The authors conclude that hyperpyrexia alone is not a satisfactory method of treatment of early syphilis and interpret the failure as due to the impossibility of raising the temperature of the skin and mucosae to the thermal death point of the virus.

122. Bierman, W., and Fishberg, E. H.: Some Physiologic Changes During Hyperpyrexia Induced by Physical Means, *J. A. M. A.* **103**:1354 (Nov. 3) 1934.

123. Bishop, F. W.; Lehman, E., and Warren, S. L.: A Comparison of Three Electrical Methods of Producing Artificial Hyperthermia, *J. A. M. A.* **104**:910 (March 16) 1935.

124. Mortimer, B., and Osborne, S. L.: Tissue Heating by Short Wave Diathermy, *J. A. M. A.* **104**:1413 (April 20) 1935.

125. Epstein, N. N., and Cohen, M.: The Effects of Hyperpyrexia Produced by Radiant Heat in Early Syphilis, *J. A. M. A.* **104**:883 (March 16) 1935.

Whether the association of heat and chemotherapy will prove to be of greater value in the treatment of early syphilis than chemotherapy alone, as suggested by the experimental studies and clinical trials of Richet and Dublineau,¹²⁶ can be determined only by further study. Probably the discomfort, loss of time and actual risk surrounding fever therapy will render it of limited application in patients with early syphilis, who after all are not incapacitated by their disease.

Mechanism of Action of Fever Therapy and of Chemotherapy in Syphilis.—Levaditi and his associates¹²⁷ tried the effect of short wave diathermy in spirillosis of the chicken, infection of the mouse with *Trypanosoma Evansi*, toxoplasmosis of the rabbit caused by *Toxoplasma cuniculi*, polyarthritis of the mouse due to *Streptobacillus moniliformis*, rabies, herpetic infection in the mouse, encephalitis in the mouse caused by the virus of venereal lymphopathy and experimental syphilis in the mouse and rabbit. On spirillosis of the chicken, recurrent fever of the rat and mouse, trypanosomiasis, rabies and polyarthritis and herpes of the mouse there was no effect. In about 50 per cent of cases of toxoplasmosis there was a favorable influence and in those of encephalitis due to the virus of venereal lymphopathy there was an inconstant favorable influence. Thus, on acute infections which are usually promptly fatal there was no effect.

In syphilis the curative and preventive action of fever therapy by short wave diathermy is incontestable. The authors started first by demonstrating that normally the temperature of the testicular chancre is constantly from 4 to 5 C. lower than the rectal temperature and that at the height of fever, when the rectal temperature is from 42 to 43 C., the highest temperature of the testicular syphiloma is 39.6 C. This is below the level which other authors have shown to be spirochetidal in vivo or in vitro (41 to 42 C.).

The activity of fever therapy is shown by rapid healing of the chancre, by the disappearance of spirochetes, by morphologic modification of the remaining spirochetes, by sterilization of the lymph nodes and of the brain and finally by frequent negative reactions of serologic tests. Unhappily, however, these therapeutic and prophylactic effects are far from being constant. With difficulty one can prevent infection in from about 50 to 60 per cent of rabbits. In the mouse in spite of a great

126. Richet, C., Jr., and Dublineau, J.: *Pyréto et chimiothérapie associées dans le traitement de la syphilis du lapin*, J. de physiol. et de path. gén **31**:794, 1933. Richet, C.; Dublineau, J., and Joly, F.: *Pyréto et chimiothérapie associées dans la syphilis primaire et secondaire: étude expérimentale et clinique*, Presse méd. **2**:649, 1933.

127. Levaditi, C.; de Rothschild, H., and others: *Etude expérimentale de la thermothérapie générale par les radiations à ondes courtes*, Ann. Inst. Pasteur **52**: 23, 1934.

number of treatments the lymph nodes continue to contain spirochetes, which are easily demonstrable on section and are virulent.

It is thus certain that an individual factor enters the picture in one sense or another to influence the curative or preventive activity of treatment with heat. Success depends on the individual patient, the moment of starting treatment and the degree of the morbid process. Thus, short wave irradiation and probably also fever treatment in general act not directly in suppressing the pathogenic activity of the organism of the disease but indirectly by the intermediation of the organism which harbors this agent. The heat either facilitates or provokes sterilization by augmenting the defensive ability of the humoral or cellular mechanism which the organism brings into play toward spontaneous cure. In this respect fever treatment does not differ from chemotherapy. Modern research tends to confirm more and more the conception formulated by Levaditi in 1908 to the effect that chemotherapeutic agents play the rôle of catalyzers in respect to the principles which insure the destruction of germs and the sterilization of the tissues. Heat may be one of the active factors, but it is not all. Other curative elements enter in of which nothing is known, but which physiologic and physical investigation will some day disclose. Whatever may be the mechanism of heat treatment by short wave diathermy, its activity is far less under the circumstances of these experiments than that of various drugs.

In a speculative discussion Dustin¹²⁸ arrives at similar conclusions as to the chemotherapy of syphilis. Ehrlich expressed his belief in the direct toxic action of drugs on the parasite. Modern investigators, however, consider that this explanation is too simple and that the pharmacodynamic action of drugs is due to the inciting of complex humoral and cellular mechanisms. The principal objection to the simple explanation rests in the fact that in vivo the drug is present in a dilution so considerable that it is completely inactive on parasites studied in vitro. From this fact it is necessary to deduce as a working hypothesis that the parasitocidal action of a drug results not from direct parasitotropism but from the production of new substances from the combination or from the conflict of the injected drug with different albumins in the body.

In a long series of remarkable papers Levaditi and his collaborators have produced important facts bearing on this hypothesis. In 1905 Levaditi showed that sodium arsaniolate is incapable of destroying trypanosomes in vitro but becomes very active after incubation with a fresh extract of rabbit liver. An arsenicalized toxalbumin is manu-

128. Dustin, A. P.: Quelques aperçus anatomo-pathologiques sur le mode d'action des produits chimiothérapeutiques, Bruxelles-méd. **13**:1035, 1933.

factured by the organism at the expense of the arsenic. This derivative which is so active in vitro is, however, void of preventive or curative action in vivo. This difference is apparently due to the fact that the newly formed substance has a great affinity for a series of tissues on which it fixes itself, particularly red blood cells, liver and spermatozooids. Similar results have been obtained with antimony, bismuth and tryparsamide. The lysis of the spirochete demands only infinitesimal traces of metal.

Dustin says that the action of certain chemical substances and that of radiation are identical in that neither is direct. The chemicals are much less active on cells or organisms observed in vitro or on tissues the blood supply of which is temporarily interrupted or reduced by epinephrine.

The discovery of the reticulo-endothelial system enters into this discussion. This system is present throughout the entire organism, is more abundant at certain points (connective tissue, the sinusoids of the liver, lymph glands, spleen and bone marrow) and possesses the fundamental property of taking up and holding fine particles in suspension, particularly those of exogenous origin (such as india ink, carmine, pyrrol blue or a bacterial suspension) or of endogenous origin (such as hemosiderin, lipoids and pigments). These cells that are capable of fixing noxious substances or bacterial suspensions should play a prime rôle in the defense of the organism against infections and in the development of the phenomena of immunity. The extraordinary success which has met this conception and the enormous amount of work which has been done on it are well known. However, this conception leaves a good deal to be desired.

In 1923 Bieling noted that the formation of antibodies was greatly diminished in splenectomized animals on blockage with saccharate of iron. In 1927 Kritchevsky noted that blockage in the mouse diminished the action of the arsenicals. In the same year Jungenbluth found that in mice in which there had been blockage with saccharate of iron, infection with spirochetes or trypanosomes was much more grave and more resistant to treatment. Feldt and Schott obtained similar results, though others, for example Schlossberger and Prigge, expressed the opinion that the reticulo-endothelial system played no rôle in the action of the drug. Collon has shown that so-called blockade of the reticulo-endothelial system is without effect on the development of immunity, on the reserve of alexin or on the formation of precipitous agglutinins, hemo-agglutinins or antitoxins. Dustin is of the opinion that the influence of the reticulo-endothelial system has been exaggerated and that a great deal more work is necessary on this point.

Dustin has worked experimentally with the thymus gland in a number of different animals and for a number of different purposes; but in the course of these experiments he has noted that animals treated with drugs, including the arsenicals, showed very interesting changes in the thymus gland and in the lymph nodes, spleen and tonsils. Histologic studies of the organs after treatment with these drugs showed the destruction of an enormous number of cells, the appearance of phagocytes and intracellular digestion of the débris and presumably the liberation of nucleolytic ferments and a whole series of products of disintegration not well known, and in addition important disturbances of the mitotic rhythm—sometimes by violent excitation of cell division, sometimes by too prolonged suspension. These cellular changes may play a very great part in the chemotherapeutic activity of injected drugs.

In spite of the suggestion conveyed by Dustin's work and in the literature cited by him that the reticulo-endothelial system influences the effect of antisyphilitic drugs, Pockels,¹²⁹ working in Kolle's laboratory, was unable to confirm this hypothesis. He conducted an elaborate series of experiments involving trypanosomal and spirochetal infections in mice and rabbits and interference with the reticulo-endothelial system by various procedures, none of which had any demonstrable effect on the therapeutic activity of the arsphenamines.

These three studies are cited at length because they illustrate the uncertain basis of the present knowledge of the mechanism of treatment in syphilis and the trend of opinion in the direction that a larger part of that effect consists in the stimulation of the patient's own power of defense.

The Physiology of Electropyrexia.—In an effort to explain why the fever treatment of syphilis is often successful in the late stages but is not in the early stages, Neymann and Osborne¹³⁰ determined by means of specially contrived instruments that artificial fever raises the temperature of internal organs (liver, cisterna magna, spinal canal, rectum and colon) 2 F. higher than the subcutaneous temperature of the thorax and abdomen and that in the extremities the subcutaneous temperature is proportionately even lower. Since the thermal death point of *Spirochaeta pallida* is 42 C. (107.6 F.) maintained for from one to six hours, since internal temperatures of 109.6 F. are not practicable in human beings and since in early syphilis the virus is abundantly present in the

129. Pockels, W.: Experimentelle Studien über die Wirkung des Retikuloendothels auf die Toxizität und die Heilwirkung der Arsenobenzole, Arb. a. d. Staatsinst. f. exper. Therap. **29**:12, 1934.

130. Neymann, C. A., and Osborne, S. L.: The Physiology of Electropyrexia, Am. J. Syph. & Neurol. **18**:28, 1934.

skin and superficial mucosae, the poor results of fever therapy in the early stages of syphilis are readily explained.

In addition, these authors point out that during the induction of artificial fever there is a marked loss of fluids and chlorides owing to perspiration. The administration of sweat-inhibiting drugs causes delirium; the basal metabolic rate rises an average of 7 per cent for each degree Fahrenheit of increase in temperature; there are concentration of the body fluids and a consequent increase in red and white blood cells and in the nonprotein nitrogen and uric acid contents of the blood during fever, and the systolic blood pressure rises and the diastolic pressure falls.

Fever Therapy of Neurosyphilis with Vaccine.—Schnitker¹³¹ reports that in 25 patients the use of typhoid H antigen vaccine combined with trypanamide produced symptomatic and serologic improvement comparable to that obtained by other forms of fever therapy. The interest of this paper lies in the pyrogenic agent used—"a water-clear saline filtrate containing the flagellar (H) antigen of the organism, the somatic (O) antigen having been blocked by phenol." The paroxysm of fever produced by it is relatively constant in all persons. It differs from that of whole typhoid vaccine in that the rise of temperature is more constant, slightly higher and more prolonged, and it has the special advantage of being less violent (i. e., the patients are not nearly so sick).

Fever Treatment of Dementia Paralytica.—Cullins, Morgan and Seymour¹³² express the belief (on the basis of 205 patients treated) that diathermy treatment of dementia paralytica is less satisfactory than induced malaria, but that mechanical fever has a distinct place in therapy, second only to that of malaria.

Results of Malarial Therapy of Neurosyphilis.—The most interesting and satisfactory reports of the results of malarial therapy of neurosyphilis appearing in recent months are those of Freeman, Eldridge and Hall,¹³³ O'Leary and Welsh¹³⁴ and O'Leary.¹³⁵

131. Schnitker, M. T.: Treatment of Dementia Paralytica with Typhoid H Antigen Vaccine, Arch. Neurol. & Psychiat. **31**:579 (March) 1934.

132. Cullins, J. G.; Morgan, H. P., and Seymour, W.: Superdiathermy in Treatment of Dementia Paralytica, M. Bull. Vet. Admin. **11**:217, 1935.

133. Freeman, W.; Eldridge, W. W., and Hall, R. W.: Malaria Treatment of Dementia Paralytica: Results in Two Hundred and Five Cases After Five to Eleven Years, South. M. J. **27**:122, 1934.

134. O'Leary, P. A., and Welsh, A. L.: Treatment of Neurosyphilis with Malaria: Observations on 984 Cases in the Last Nine Years, J. A. M. A. **101**: 498 (Aug. 12) 1933.

135. O'Leary, P. A.: Asymptomatic Neurosyphilis, South. M. J. **28**:47, 1935; Malaria Therapy in Asymptomatic Neurosyphilis, Ann. Int. Med. **7**:1513, 1934.

Freeman and his co-workers followed up 195 of a series of 205 patients treated for dementia paralytica for from five to eleven years after the completion of malarial treatment. Of those traced, 31 per cent were discharged from the hospital (i. e., in complete or nearly complete remissions), 39 per cent remained hospitalized and 30 per cent died. The remissions obtained showed indications of being permanent, and the percentage of recoveries has not declined notably with the passage of years. The good results obtained were in reasonably direct proportion to the number of paroxysms of fever, and the authors express the belief not only that less than ten paroxysms are relatively futile but that as many paroxysms as the patient can safely tolerate should be allowed.

O'Leary and Welsh report on the status of patients treated with malaria who had a wide variety of types of neurosyphilis. Excellent clinical results were obtained as follows: advanced dementia paralytica, 35 per cent; early dementia paralytica, 46 per cent; asymptomatic neurosyphilis with the "paretic formula" in the cerebrospinal fluid ("asymptomatic paresis"), 78 per cent; tabetic dementia paralytica, 55 per cent; tabes dorsalis (general group), 42 per cent; gastric crises with negative reactions of the cerebrospinal fluid, 31 per cent; intractable lightning pains with negative reactions of the spinal fluid, 11 per cent, and primary atrophy of the optic nerve, 14 per cent. The authors express the belief that malarial treatment is indicated not only for patients with dementia paralytica but also and particularly for patients with other forms of syphilis who are not responding favorably to other types of antisyphilitic treatment.

O'Leary was especially impressed with the value of malarial treatment in 89 cases of asymptomatic neurosyphilis, and in two communications he points out that in 50 per cent of patients whose spinal fluid fails to become normal after therapy with arsphenamine, bismuth, mercury and subdural injections, serologic normality (apparently permanent) may be achieved by means of malarial treatment. Fever therapy is therefore of the utmost value in the prevention of parenchymatous neurosyphilis as well as in its treatment.

Malarial Therapy.—The relationship of blood grouping to induced malaria is discussed by Polayes and Derby¹³⁶ on the basis of a review of the literature and personal experience with 127 patients. When the donor's blood is compatible, the incubation period of malaria in the recipient is halved (to an average of four and three-tenth days). The question of minor reactions of incompatibility and of so-called primary fever (i. e., remittent fever preceding the development of frank paroxysms) also are discussed.

136. Polayes, S. H., and Derby, I. M.: Blood Groups and Therapeutic Malaria, J. A. M. A. **102**:1126 (April 7) 1934.

The Reactivation of Malaria.—Every physician who treats patients with neurosyphilis is familiar with the premature spontaneous abortion of induced tertian malaria which occurs, depending on the strain employed, in from 5 to 10 per cent of patients treated. Epinephrine, typhoid vaccine given intravenously and cold baths have been used with varying success in the attempt to reactivate the paroxysms of fever in such patients. Videla,¹³⁷ working with natural and induced malaria, was successful in reactivating a latent infection in 4 of 6 patients by means of the daily intravenous injection of 10 cc. of a 10 per cent solution of calcium chloride (from one to three injections were necessary). The mechanism by which this result is produced is not clear, but the method is worthy of further trial.

The Untoward Effects of Malarial Therapy.—Karnosh and Williams¹³⁸ review the complications of malarial therapy in 580 patients with dementia paralytica and describe an untoward sequel not heretofore stressed, characterized by hemorrhages, hematomas and noninflammatory ulcers of the intestine, which they regard as specific lesions due to malaria. This complication occurred in 5 patients, all of whom died, and in each the specific lesion was found at necropsy. Shirokogorov¹³⁹ studied the interrelationship between malaria and pulmonary tuberculosis at necropsies on 800 patients who had died of acute or chronic malaria (not induced) and found no evidence that malaria reactivated a primary tuberculous focus.

The Treatment of Malaria.—Craig¹⁴⁰ provides a review of the present status of atabrine (an acridine derivative) and plasmochin (N-di-ethylamino-iso-pentyl-8-amino-6-methoxyquinoline), which will be valuable to all physicians utilizing malarial therapy.

MAPHARSEN

"Mapharsen" is the producer's name for meta-amino-para-hydroxyphenylarsine oxide. This drug, an exceedingly potent and toxic arsenical, was studied by Ehrlich and abandoned because of its toxicity. It is considered to be the therapeutically effective breakdown product of all of the arsphenamines. Experimental and clinical study of this interesting drug has been taken up afresh by the Wisconsin group of investi-

137. Videla, C. A.: *Reactivation of Latent Malaria by Calcium Chloride Injections*, Prensa méd. argent. **21**:2378, 1934.

138. Karnosh, L. J., and Williams, G. H.: *Some Unusual Complications in Malaria Therapy*, Ohio State M. J. **31**:193, 1935.

139. Shirokogorov, I. I.: *Effect of Malaria on Pulmonary Tuberculosis*, Klin. med. **12**:1786, 1934.

140. Craig, C. F.: *Results of Recent Research in the Treatment of Malaria*, South. M. J. **27**:546, 1934.

gators. To date only a portion of their experimental work has been published. Tatum and Cooper¹⁴¹ show that this drug is a pure chemical preparation the purity of which is readily determinable by chemical methods, whereas the arsphenamines are chemical mixtures which may vary with each lot and therefore require biologic assay. Mapharsen increases in toxicity only slowly on oxidation. The minimum lethal dose and minimum tolerated dose, respectively, for various animals are as follows: rats, 25 and 20 mg. per kilogram of body weight; rabbits, 16 and 10 mg.; cats, 7 and 5 mg., and dogs, 15 and 10 mg. For infection of rats with *Trypanosoma equiperdum* the curative dose is 0.8 mg. per kilogram and the therapeutic index 25. For *T. rhodesiense* infections of rats the curative dose is 9 mg. per kilogram and the therapeutic index 2.2. A single dose of 6 mg. per kilogram (therapeutic index, 1.6) or three weekly injections of 0.8 mg. per kilogram (index, 12.5) is curative of rabbit syphilis. These indexes for rabbit syphilis were superior to those of two brands of neoarsphenamine studied by the same investigators. The authors are convinced that mapharsen possesses such outstanding advantages over the arsphenamines as to justify its clinical investigation. This clinical trial has been under way for several years, and the results of the use of the drug in human beings will be published shortly.

141. Tatum, A. L., and Cooper, G. A.: An Experimental Study of Mapharsen (Meta-Amino-Para-Hydroxy Phenyl Arsine Oxide) as an Antisyphilitic Agent, *J. Pharmacol. & Exper. Therap.* **50**:198, 1934.

CORRECTION

In the article by Dr. Walter M. Boothby, entitled, "Disease of the Thyroid Gland: An Interpretative Review of Progress Toward Solution of the Problem," in the July issue (*ARCH. INT. MED.* **56**:136, 1935), "approximately 25 mg." in the thirteenth line on page 160 and in the tenth line on page 161 should read "approximately 250 mg."

Book Reviews

The Clinical Aspects of Visceral Neurology, with Special Reference to the Surgery of the Sympathetic Nervous System. By W. K. Livingston, M.D., Clinical Associate in Surgery, University of Oregon Medical School. Cloth. Price, \$5. Pp. 246, with 46 illustrations and 3 color plates. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

This book gives a brief review of the anatomy, physiology and clinical aspects of visceral surgery but, as the name implies, is written chiefly from the point of view of the surgeon with respect to sympathetic surgery. The physiologic aspect of both the normal control of the peripheral circulation and the late effects of sympathectomy are not treated sufficiently to give the reader a clear conception of these complex processes. There is some discussion regarding the skin temperature as a test of circulation, but Livingston does not impress on the reader that at best the skin temperature can be only a rough approximation of circulation, as it is well known that the skin temperature represents the sum total of a number of factors acting on the skin, of which circulation is only one. Failure to appreciate this fact and the ease of taking the skin temperature has led to unwarranted conclusions. In the discussion of poor results from sympathetic surgery in some cases of Raynaud's disease it is implied that the operation was incomplete. There is good evidence to show that in both lower animals and man the circulation of the part returns to the preoperative level in a comparatively short time after sympathetic ganglionectomy and ramisectomy, even though the operation is complete. Livingston has not thoroughly considered the factors which control the vascular tone in the absence of sympathetic vasoconstrictor tone. However, the criticisms and unfavorable impressions may have been gained from the fact that the author has attempted to cover such a tremendous and controversial field in such a small volume. The known facts regarding sympathectomy for relief of peripheral symptoms indicate that this type of surgical intervention must still be considered purely an experimental procedure. This book cannot be recommended as contributing anything but the surgical point of view of visceral surgery, but it may serve as a good outline for those interested in this field.

Chemistry of the Hormones. By Benjamin Harrow, Associate Professor of Chemistry, the City College, College of the City of New York, and Carl P. Sherwin, St. Vincent's Hospital and French Hospital, New York. Price, \$2.50. Pp. 227. Baltimore: Williams & Wilkins Company, 1934.

This book is primarily for the biochemist who wishes for a survey of the best methods for the preparation of hormones. It is not exhaustive in its treatment, but rather gives a few of the most successful methods of preparation. The reader becomes acquainted with the present state of the chemistry of hormones without the confusion which may follow when the subject is presented in detail.

Some historical material is included. The physiologic properties of the hormones are touched on briefly. There is little discussion of clinical material, and only the most significant papers are included in the bibliography.

The work is primarily a reference book. The type is large, well arranged and very readable.

APPEARANCE OF A DENGUE-LIKE FEVER IN NORTHERN CALIFORNIA

GARNETT CHENEY, M.D.

SAN FRANCISCO

Late in the spring of 1934 a patient was seen in San Francisco who presented a clinical picture like that of dengue. A syphilitic patient inoculated with his blood showed the symptoms and signs of inoculation with dengue which have been studied experimentally in many parts of the world. Subinoculations in three other successive patients reproduced the same type of illness in each. As there are no recent reports of dengue occurring in the United States and as the disease has never been recorded as occurring endemically in Northern California, the possibility of its appearing here is of great importance. Although this is the only instance to date in which an attempt has been made to substantiate the diagnosis by inoculation into human subjects, five additional cases of apparently the same condition have been recognized. These endemic cases together with the four experimentally produced ones form the basis of this report.

REPORT OF CASES

CASE 1.—On the evening of April 30, 1934, I. A., a 41 year old insurance agent, married, was seen at his home complaining of a high fever of two days' duration.

The family history and the past history were irrelevant. His type of work required that he travel all over the state of California, and he was habitually careful of his water and food supply as a precaution against typhoid and other infections. A large police dog which was occasionally sick and had ticks and fleas was almost constantly with him. Nineteen days before the onset of the present illness he removed a tick from the cubital vein of his left arm while he was in Santa Clara County. Ten days later he was bitten twice by flies near Gonzales, and the next day, nine days before his present illness, he was bitten by a mosquito at Salinas, Monterey County.

Present Illness.—On the afternoon of April 28, while the patient was driving his car from San Francisco to Palo Alto, he noted that his back was a little stiff. He slept well that night, but at 8 o'clock the next morning he suddenly grew ill and thought that influenza was developing. He drove back to San Francisco and went to bed. At the onset he felt chilly, and his bones and joints ached all over. Pain in the back was severe, "like a hot poker" or "a sacro-iliac slip." His joints became stiff, the condition being "like arthritis"; his head ached moderately, and he felt feverish. He slept fairly well, but the next day he had severe pain in the right shoulder and excruciating pains and tenderness in the lower portion of the

From the Department of Medicine, Stanford University Medical School, and the San Francisco Department of Public Health, Laguna Honda Home.

legs and in the heels. This was so pronounced that he could not stand up and had to crawl to the lavatory on his hands and knees. It felt "as if the marrow was being torn out of the bone." The temperature rose to 103 F. A chart of its course is shown in figure 1. The pulse rate varied proportionately.

On the third day the legs were better and the joints were no longer stiff but there were intense jabbing neuralgia-like pains which "felt like an ice-pick" in the right side of the face and in the right ear. These grew better on the fourth day, but the patient grew restless and irritable. On the fifth and sixth days he complained of severe prostrating headache, which was felt all through the head but was worse behind the eyes, and he had marked photophobia. He saw flashes

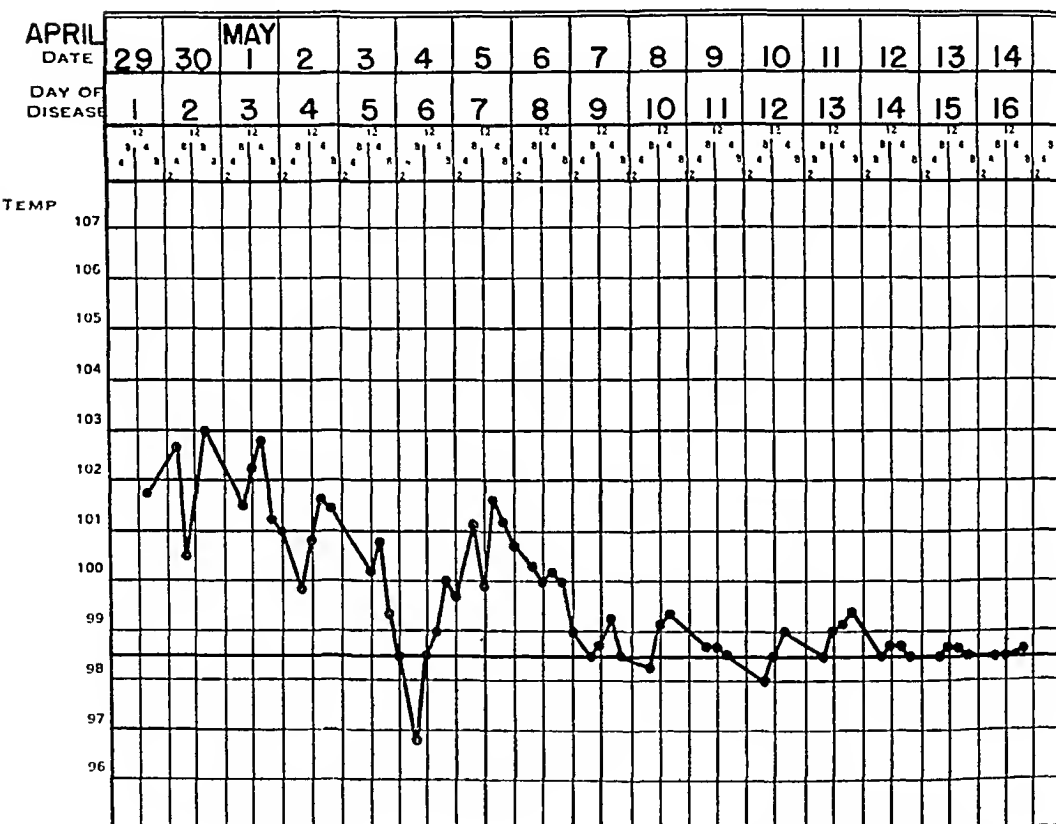


Fig. 1 (case 1).—Curve for temperature, showing biphasic form of fever.

of yellow light from time to time, as if an electric sign were turned on and off rapidly. Food had an appetizing smell but tasted bad, "like spoiled meat," and it was almost impossible for him to eat. He also had marked nausea, retching and distention and soreness in the upper part of the abdomen. There were pain and soreness in the testicles. During this time he complained of such severe itching of the hands, feet and lower portion of the legs that it was hard to keep him from scratching his skin deeply. Improvement occurred on the seventh day, and by the eighth day the patient was free from most of his troublesome symptoms.

Physical Findings During the Illness.—Examination on the evening of the second day disclosed no abnormalities except that the patient was flushed from the fever and had some tenderness of the muscles of the calves and of the heels. He was a large, well built man, was clear mentally and was not depressed or toxic.

The eyes, ears, nose, gums and throat appeared normal. The tongue had a thick creamy coating on the dorsal portion. The heart was not enlarged; the sounds were clear, and no murmurs were present. The lungs were normal. The abdomen showed no abnormalities except moderate tenderness at the left costal margin and in the epigastrium. There was marked tenderness in both lumbar regions. Although the patient complained of stiffness in the joints, particularly in those of the fingers, no signs of arthritis were present. No lymph glands were palpable in the neck, axillae or groins. The knee jerks and ankle jerks were present and equal. No cutaneous rash was present. The blood pressure was 120 systolic and 80 diastolic; the temperature was 102.8 F., and the pulse rate, 104. The bowels had moved regularly.

The findings were not materially altered until the fifth day, when there appeared frequent retching and vomiting, also tenderness and muscle spasm in the upper part of the abdomen which was most marked at the left costal margin. The face and neck became extremely flushed; the eyelids were puffy, and there was pronounced conjunctivitis. The patient was prostrated and irritable. He remained in this condition for three days and was slightly delirious on the second night. The neck was not stiff, and Kernig's sign was not present. The crushing headache was partially relieved by local pressure but was completely controlled only by opiates. On the eighth day there was much improvement, but the patient had a slight cough with a little thick, tenacious sputum. There were a few scattered râles at the base of the left lung but no signs of pulmonary infiltration. All unusual findings had disappeared by the next day except that the patient was weak and tired. There was no rash.

Laboratory Examinations.—Urine: The amount was scanty throughout the febrile period. There was only one voiding of about 100 cc. on the fifth day. The specific gravity varied between 1.024 and 1.032. The color was always high. No sugar was present. On the third day there was a light cloud of albumin, but on the fourth and sixth days the clouding was heavy. On the ninth and twelfth days a faint trace of albumin was found, and sixteen days after the onset of the illness there was no clouding. When large amounts of albumin were present the sediment showed a solid mass of hyaline and finely and coarsely granular casts occurring in such profusion that no estimate of the number could be made. Many white and red blood cells were also noted. By the sixteenth day only an occasional cast and a few cells were present.

Blood: On the third day there were 10,000 white cells, 72 per cent polymorphonuclears, 17 per cent lymphocytes, 7 per cent large mononuclears and 4 per cent transitionals. On the fourth day there were 7,000 white cells, 72 per cent polymorphonuclears, 22 per cent lymphocytes, 5 per cent large mononuclears and 1 per cent transitionals. The Schilling count showed that 57 per cent of the polymorphonuclears were banded and 43 per cent mature forms. Smears showed no malarial parasites on the fifth day. The sedimentation rate was 20 mm. in forty minutes. Cultures, including a special set-up for *Brucella abortus*, showed no growth. Agglutination tests were negative for *Bacillus typhosus*, *Bacillus paratyphosus* A and B, *Brucella abortus* of bovine, porcine and caprine strain and *Bacterium tularensis*. The icteric index was 6 units.

On the sixth day the vomitus was greenish. The total acidity was 20. Free hydrochloric acid was absent. There was no occult blood. On the eighth day examination of the stool gave negative results for occult blood and for ova and parasites.

On the fourth day of this patient's illness 5 cc. of venous blood was withdrawn and oxalated, and one-half hour later injected into a vein of another patient

(case 2). A third patient (case 3) received a similar injection of 5 cc. of whole blood from the second patient, and a fourth (case 4) received 5 cc. of whole blood from the third patient. A fifth patient (case 5) was inoculated in a similar fashion with blood from the fourth patient but in this instance the blood was withdrawn on the third day of the illness instead of on the fourth day, as in the other three cases. Two other patients with chronic encephalitis received subcutaneous injections of 0.5 cc. of serum from the first patient (case 1) which had been kept in the icebox five days and seven days, respectively. Neither of them became ill or showed any significant change in temperature or pulse rate subsequently.

As the clinical course of dengue produced by inoculation is like that of the acquired type ¹ and as the findings in the four cases of artificial

TABLE 1.—*Important Clinical Findings in the Six Cases of Endemic Dengue-Like Fever and in the Four Cases Produced by Inoculation of Whole Blood*

Clinical Findings	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Infection by inoculation.....	—	+	+	+	+	—	—	—	—	—
Sudden onset.....	+	+	+	+	+	—	+	—	+	+
Severe headache.....	+	+	+	+	+	—	—	+	+	—
Postorbital pain.....	+	+	+	+	+	+	—	+	—	+
Severe backache.....	+	+	+	+	+	+	+	+	+	—
Pains in the limbs.....	+	+	+	+	+	+	+	+	—	—
Stiffness of the joints.....	+	+	+	+	+	+	—	—	—	—
Photophobia.....	+	+	—	—	+	—	—	—	+	—
Perversion of the sense of taste.....	+	+	+	+	—	—	—	—	—	+
Suffusion of the face and neck.....	+	+	+	+	—	?	?	—	—	?
Herpes labialis.....	+	+	—	—	—	—	—	—	—	+
Vomiting.....	+	—	—	—	—	—	—	—	—	+
Severe abdominal pains.....	+	—	—	—	—	?	—	—	—	+
Enlargement of lymph glands.....	—	—	+	+	+	?	?	?	+	+
Enlargement of spleen.....	—	—	—	—	—	—	?	+	+	—
Pain in testicles.....	+	—	—	—	—	+	—	—	—	—
Rash at onset.....	—	—	—	—	—	+	?	—	?	?
Terminal rash.....	—	+	+	—	—	—	—	—	+	—
Itching.....	+	—	+	—	—	+	—	+	—	—
Biphasic fever.....	—	—	—	+	—	+	?	+	+	+
Leukopenia.....	—	—	—	+	—	+	?	—	—	+
Duration of illness in days.....	8	8	6	9	7+	8	6	7	6	7+
Râles at bases of lungs.....	+	+	+	+	—	—	?	+	—	—
Jaundice.....	—	—	+	—	+	—	—	—	—	+
Albuminuria.....	+	+	?	—	—	—	?	—	—	—
Sequelae.....	—	+	+	—	+	+	—	+	—	+

infection closely resembled those in the endemic ones, the important symptoms and findings are recorded together for both groups in table 1, and detailed descriptions of the experimental series are omitted. The results of the white cell counts are listed in table 2 and shown graphically in figure 2. The four patients who were inoculated had syphilis of long standing; their blood showed strongly positive Wassermann and Kahn reactions, and they were hospitalized as possible candidates for malarial therapy.

CASE 2.—A. G. P., 50 years old Estonian, single, had been hospitalized eight months previously on account of a stroke and partial loss of vision. He was inoculated on May 2, 1934, and ninety-two hours later there appeared fever, which lasted eight days. On the sixth day there developed an extensive macular rash over the shoulders and the entire trunk, which lasted six days. The "spots" varied in diameter from about 1 mm. to 1 cm. and were of a dusky red hue, gradually

fading out without any desquamation. As the curve for temperature is much like that observed in cases of so-called saddleback fever, it is shown in figure 3. After this attack of fever it was noted that the patient was quiet and drowsy for three weeks. He complained of photophobia and fulness and aching in the head and "sleeping twenty hours a day." His normally restless irritable disposition was in strong contrast to the present docile lethargic state. When allowed to lie in bed he slept almost constantly. After the first week he had daily rises of temperature

TABLE 2.—*White Blood Cell Counts in Nine Cases of Dengue-Like Fever*

Case No.	Day of Illness	White Cell Count	Differential White Cell Count, Percentage							Baso-phils
			Poly-morpho-nuclears	Staff Cells	Seg-mented Cells	Lympho-cytes	Transi-tional Forms	Large Mono-cytes	Eosino-phils	
1	3rd	10,000	72	42	30	17	4	7	—	—
	4th	7,000	72	41	31	22	1	5	—	—
2	5th	7,800	70	—	—	30	—	—	—	—
	7th	8,400	64	34	30	30	—	4	2	—
	9th	16,350	40	10	30	50	1	6	3	—
	11th	15,900	45	12	33	46	5	4	—	—
	22nd	10,350	55	5	50	38	2	—	5	—
3	2nd	9,750	64	20	44	33	1	2	—	—
	3rd	11,800	75	30	45	25	—	—	—	—
	4th	16,000	84	60	24	15	—	1	—	—
	6th	23,350	81	45	36	18	—	1	—	—
	7th	30,000	77	51	26	21	—	2	—	—
	9th	18,700	85	—	—	15	—	—	—	—
4	2nd	4,350	53	37	16	40	1	6	—	—
	3rd	6,450	64	13	51	19	2	3	12	—
	4th	3,800	—	—	—	—	—	—	—	—
	5th	3,000	72	36	36	26	—	2	—	—
	6th	3,600	71	37	34	26	—	1	1	1
	7th	5,210	40	26	14	50	2	4	2	2
	9th	7,900	70	33	37	28	1	—	1	—
5	1st	10,250	57	21	36	41	—	2	—	—
	2nd	17,100	69	39	30	31	—	—	—	—
	4th	6,150	78	38	40	22	—	—	—	—
	5th	8,100	64	38	36	36	—	—	—	—
	7th	20,100	45	10	35	50	2	2	1	—
	8th	23,450	57	10	47	40	—	—	2	1
	11th	28,650	58	10	48	40	2	—	—	—
	13th	17,300	58	20	38	40	1	—	—	1
	15th	24,500	56	16	40	42	2	—	—	—
6	18th	16,850	58	10	48	40	—	—	2	—
	4th	8,000	72	—	—	26	—	1	—	1
	5th	6,350	50	—	—	50	—	—	—	—
	6th	5,400	—	—	—	—	—	—	—	—
8	9th	5,800	—	—	—	—	—	—	—	—
	4th	10,700	89	42	47	6	—	5	—	—
9	7th	9,000	80	58	22	14	—	4	1	1
	2nd	6,600	75	33	42	18	—	6	—	1
10	3rd	4,250	67	35	32	27	—	4	1	1
	5th	4,900	55	26	29	41	—	4	—	—
	10th	4,100	57	23	34	40	3	—	—	—

for two weeks from 99 to 100.5 F. and on one occasion to 101.6 F. The examination of the eyegrounds, general physical examination and neurologic examinations showed nothing unusual. On May 23, after the patient had been lethargic for ten days and febrile for three days, a lumbar puncture was performed. The fluid was clear and colorless, and the pressure was 255 mm. of water. There were 33 cells, all but 2 of which were lymphocytes, per cubic millimeter of fluid. There were 58 mg. of total protein and 59 mg. of sugar per hundred cubic centimeters. The Lange reaction was 0000000000. Three months previously the findings in the spinal fluid, including the Wassermann reaction, had been entirely negative. Thirty minutes after the puncture 3 cc. of spinal fluid was injected into the vein of a

volunteer. No reaction to this injection developed during one month of close observation. The patient gradually returned to his prefebrile state.

CASE 3.—J. B., a 64 year old Greek, single, had been under observation in the hospital twice, a year previously, with a diagnosis of gastric crises with slight jaundice. He was inoculated on May 9, 1934, and ninety-six hours later the temperature rapidly rose to 102 F. It reached 104 F. on the third day and exceeded 103 F. during the next twenty-four hours. It gradually dropped to subnormal on the seventh day. On the sixth day there was a dusky mottling of the skin over the shoulders and trunk and the scleras were slightly icteric. The temperature was subnormal for two days, but marked tenderness and spasm developed in the right upper quadrant of the abdomen; the jaundice became intense, and the patient sank rapidly into a deep coma. The course of the icteric index is shown in

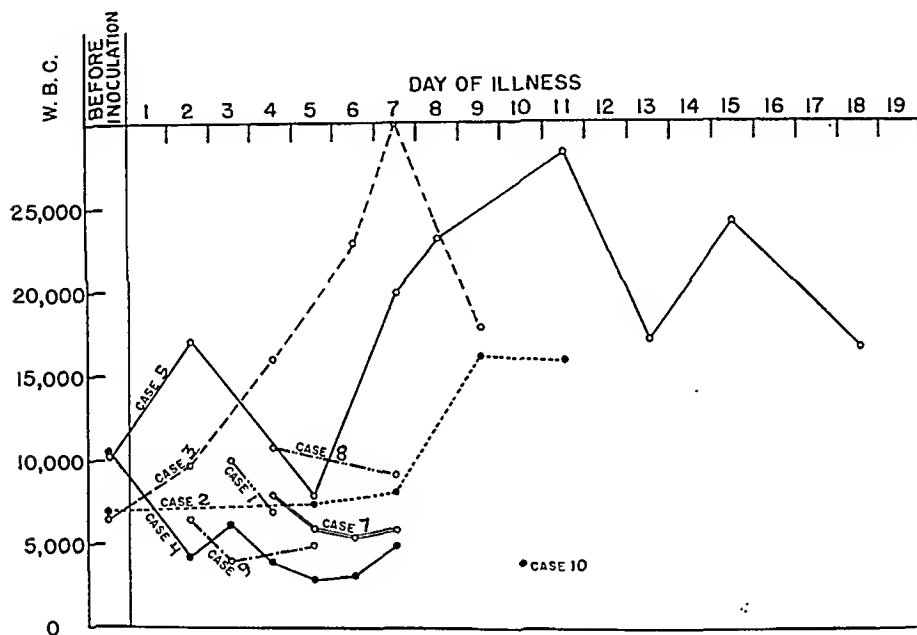


Fig. 2.—Course of the white blood cell counts in eight cases. In the only three (cases 2, 3 and 5) in which leukocytosis was present, the disease was produced by inoculation and was complicated by hepatitis in two and by encephalitis in one.

figure 4. Râles appeared in both lungs; on the third day after the attack of fever there was a terminal rise in temperature of 100 F., and the patient died.

Necropsy.—Macroscopic Examination: The body was that of a well nourished, markedly jaundiced man about 65 years of age. The upper jaw was edentulous. None of the superficial lymph glands were palpable. The thorax was of the emphysematous type. The heart was slightly enlarged, and there was dilatation of all the chambers. No lesions of the valves were found, but the coronary arteries showed many calcified atheromatous plaques, which markedly encroached on the lumens but did not produce complete occlusion. The arch of the aorta was normal in size, and its walls showed longitudinal wrinkling of the intima and a few atheromatous plaques and superficial ulcerations. Both lungs showed small old apical scars. A cut section showed marked congestion and edema, with many elevated consolidated hemorrhagic areas throughout but most marked in the lower lobes of both lungs. The bronchi were filled with frothy blood-tinged fluid.

The pleura and the pericardium were normal. The lower border of the liver extended 3 cm. below the right costal margin and 6 cm. below the xiphoid process. The liver measured 26 by 18 by 8 cm., and the surface was icteric and finely granular. The cut section was opaque. The gallbladder contained a few cubic centimeters of thin white fluid and 30 small black stones averaging 2 mm. in diameter. Its wall was thickened and the mucosa was replaced by fibrous tissue. No stones were present in the ducts. The spleen was of normal size, and was firm and smooth. The cut surface revealed congestion and prominent malpighian bodies. Examination of the pancreas, stomach and small bowel revealed nothing unusual. The large bowel was normal except for many small diverticula, which were most numerous in the transverse colon. Both kidneys were buried in fat. The capsules stripped easily. The surface showed a marked irregular granular

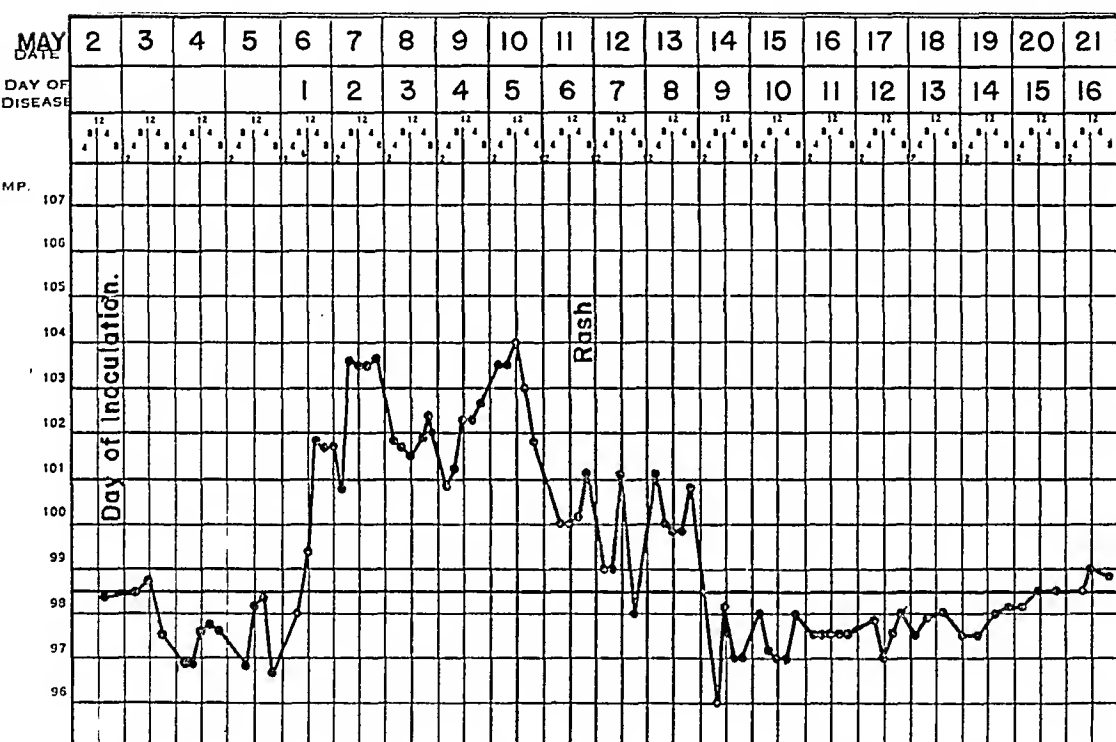


Fig. 3 (case 2).—Curve for temperature showing the characteristic abrupt onset of fever and its limited course. The disease was produced by inoculation with blood from I. A. (case 1).

appearance, and sections showed irregular areas of cloudy swelling. Both adrenal glands were normal except for congestion of the medulla. The urinary bladder and prostate were not remarkable. The brain was not examined.

Microscopic Examination: The heart showed many dense fibrous scars scattered throughout the myocardium. The media of the aorta was heavily infiltrated with round cells. Most of the alveoli of the lungs were filled with red blood corpuscles and a few polymorphonuclear leukocytes. Some of the alveoli contained many leukocytes and red cells enmeshed in fibrin. The liver cells (fig. 5) were separated from each other, and most of them had lost their nuclei except a few at the periphery of the lobules and near the capsule. Deeper in the liver only a few nuclei were to be seen. The cells stained poorly. Some of the cells about the central veins contained a small amount of brown granular pigment.

Some of the sinuses near the surface of the liver were filled with red blood cells but were only slightly dilated. The arteries showed a rather marked thickening of the intima, and there was an increase of fibrous tissue in the periportal regions and about the bile ducts. The bile ducts were lined by columnar epithelium which stained well but was detached and filled the lumen in most places. The capsule showed slight fibrous thickening.

A section stained with phyloxin (a carmine red dye used in 1 per cent solution) to bring out nuclear detail showed the remaining nuclei to contain acidophilic masses at the periphery of the nucleus. There was usually one, and sometimes there were two, of these masses, but nothing resembling inclusion bodies could be demonstrated. The Kupffer cells showed no changes.¹

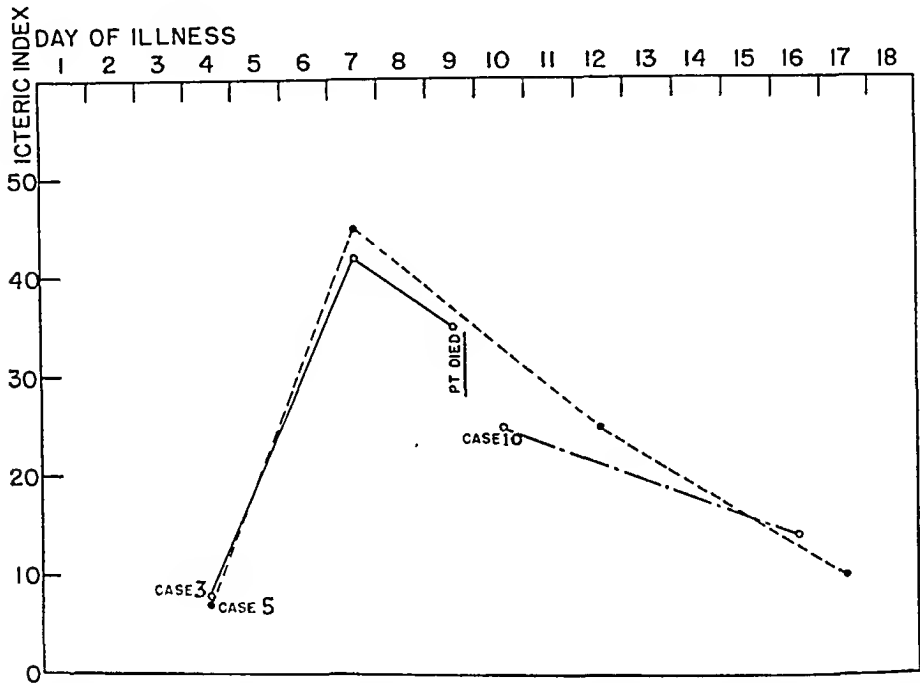
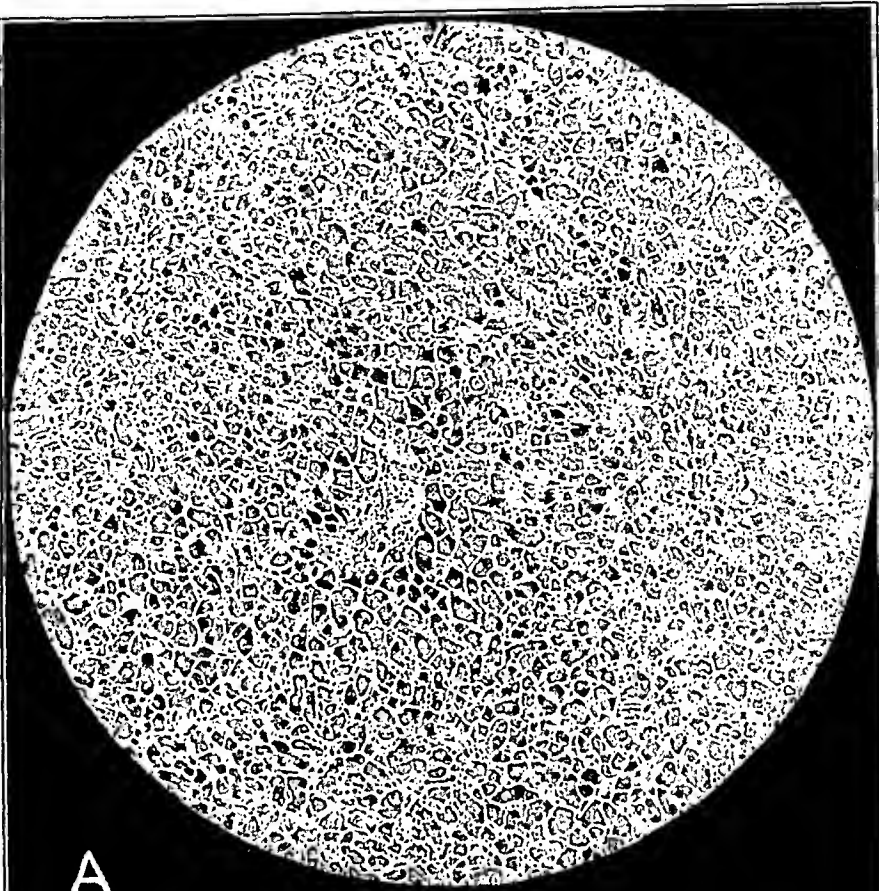


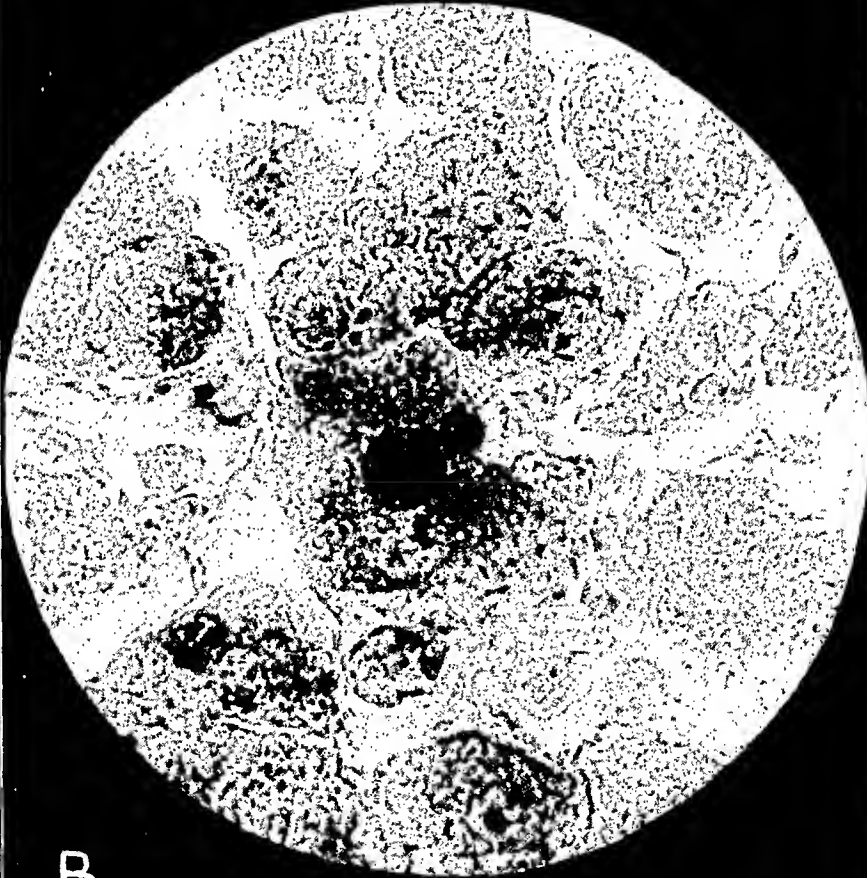
Fig. 4.—The course of the jaundice as measured by the icteric index in the three cases in which hepatitis occurred as a complication.

The walls of the gallbladder showed marked fibrous thickening with a few areas of round cell infiltration. Many of the pulp cells of the spleen were swollen and had lost their nuclei, but there was no evidence of necrosis. The renal cortex contained scars heavily infiltrated with round cells. Most of the epithelial cells of the convoluted tubules had lost their nuclei and were swollen and desquamated into the lumen. The tufts of some of the glomeruli were swollen and edematous and were moderately infiltrated with round cells and a few polymorphonuclear leukocytes. The arterioles showed a moderate fibrohyaline thickening of the intima. The sections of bone marrow showed a moderate increase in the extent of the reticular stroma and blood-forming cells. The sinusoids were filled with erythrocytes. Normoblasts were present in considerable numbers throughout the reticulum and were collected in rather extensive clusters at some points. Smears showed an increase in relative numbers of normoblasts, and mitotic figures were numerous.

1. Dr. James Owmby Jr. made special studies of the hepatic tissue.



A



B

Fig. 5 (case 3).—Photomicrographs of a section from the liver: *A*, lower magnification ($\times 100$) showing diffuse toxic necrosis; *B*, high magnification ($\times 800$) showing loss of normal structure of hepatic cells, only an occasional nucleus remaining.

Leukocytic marrow cells were numerous and showed normal developmental forms. There was a relative numerical increase of leukocytes in the more mature stages. There was no evidence of any marked hyperplasia of leukocytic cells.

Anatomic Diagnosis.—The diagnosis was acute toxic necrosis of the liver, gallstones, chronic cholecystitis, bronchopneumonia, general arteriosclerosis, severe local arteriosclerosis of the coronary arteries, with scars in the heart, diverticulosis of the colon, syphilitic involvement of the aorta and hyperplasia of erythropoietic cells in the bone marrow.

CASE 4.—W. D. B., a 63 year old English plasterer, divorced, had been under observation for eight months with clinical and roentgen evidence of Paget's disease and a broken-down gumma of the left shin. He received the inoculation on May 19, 1934, and eighty-eight hours later his temperature began to rise. In

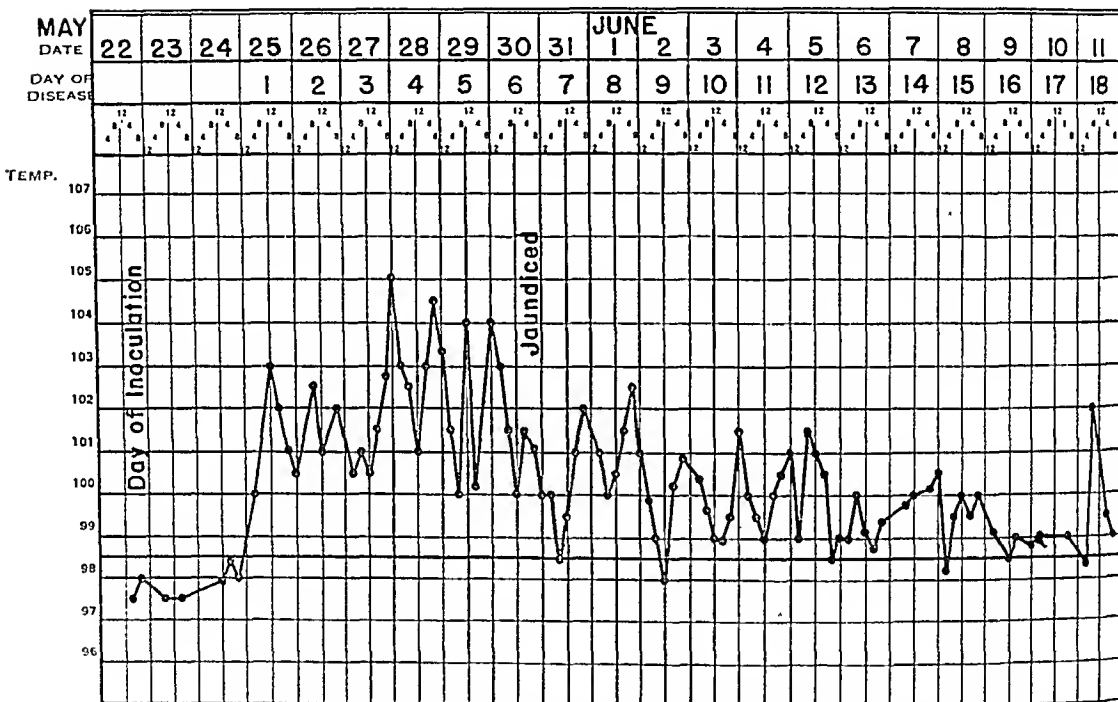


Fig. 6 (case 5).—Curve for temperature, showing a short period of incubation, high fever, jaundice and persistent pyrexia. The disease was produced by inoculation with blood from W. D. B. (case 4).

twelve hours it reached 103.5 F.; for the next twelve hours it remained at 103 F. or just above that level, and it then fell in four hours to 97.4 F. For the next eight days it rose and fell rapidly and irregularly between the normal level and 102 F. On the ninth day of the illness it dropped in eight hours from 101.8 to 98 F. and remained normal or subnormal thereafter except for one rise to 99 F. three days later. The patient insisted on being up and about during the latter part of the illness, and rapid improvement was noted.

CASE 5.—L. H., a 60 year old German, single, had been under observation for three months with arteriosclerosis, hypertension, slight mental disturbance and changes in the cerebrospinal fluid indicative of syphilis of the central nervous system. He was inoculated on May 22, 1934, and sixty hours later the temperature began to rise. The course of the fever is shown in figure 6. The tempera-

ture fell to normal for the first time on the seventh day, which might represent the end of the usual course of the disease, but fever was present daily for two additional weeks; this seemed to be due to the complicating hepatitis. The scleras appeared yellow on the sixth day, and there was clinical evidence of jaundice for ten days in all, although the liver was not palpable and not tender. The course of the icteric index is shown in figure 4. The patient was allowed to be up and about after the fever subsided, and he seemed as well as previously. On the second day of this patient's illness blood was taken for inoculations into animals. Five mice were given intraperitoneal injections of 0.2 cc. of serum, and one guinea-pig received an intraperitoneal injection, and two others, intracerebral injections, of 0.3 cc. of serum. One rabbit was inoculated intracerebrally with a like amount of serum, and one Java monkey and one *Macacus rhesus* monkey were similarly inoculated with 1 cc. of serum each. In none of the animals did any recognizable symptoms develop.

The five patients whose illness is described were all infected with the same organism, and each was carefully observed throughout the clinical course of the disease. The five patients with similar manifestations which have since come under observation seemed to have the same disease, and in each instance no definite diagnosis of any commonly recognized condition could be established. The cases are reported as completely as possible.

CASE 6.—R. N., a 22 year old Japanese housewife, complained of generalized pains on June 6, 1934. The family history and past history were irrelevant. Catamenia was said to be regular. She had not been out of San Francisco for six months. She was almost constantly troubled by flea bites. For two days before the onset of the pains she had a generalized cutaneous rash "like hives." Her physician thought that it was urticaria, but epinephrine did not afford relief. The rash subsided, but the next day the patient had intense pains "in the muscles and joints and all over from the neck down, so she could not move." A severe frontal headache was also present. Prostration was marked. The temperature rose to 103 F. on the second day. The pains in the limbs were so marked that the physician suspected trichinosis and made a blood count. The white cells numbered 8,000, and no eosinophils were found. On the third day she was free from pain and much improved, although the temperature was 101 F. On the fifth day the severe headache returned; the temperature rose to 103.5 F., and the patient seemed so ill that she was sent to the hospital.

Physical examination showed a flushed well nourished Japanese woman complaining of severe frontal headache and cramps in the lower part of the abdomen. The conjunctivae were slightly injected. The pupils were normal. No evidence of infection was found in the nose and throat. The neck was not stiff. The heart and lungs were not remarkable. The lower portion of the abdomen was tender to pressure, but no masses or organs were palpable. Pelvic examination suggested an early stage of pregnancy with danger of abortion. The deep reflexes of the legs were not unusual. Enlarged lymph glands could be readily felt in the right post-auricular region, on both sides of the neck, in the left axilla and in both groins. During the next three days there was gradual improvement except for the onset of such severe itching of the extremities that the patient could not sleep at night and scratched her skin deeply. The temperature varied between 102 F. and 103 F. on the first two days in the hospital; it averaged about 101 F. on the third day and was normal for the first time on the fourth day of hospitalization, which was the

eighth day of the illness. There were two slight subsequent rises in the next thirty-six hours before the temperature remained normal. The pulse rate varied in proportion to the severity of the fever, and the respiratory rate was not increased. No cutaneous rash occurred during the patient's stay in the hospital. The itching persisted for about a week, and about two weeks after this illness the patient aborted at home.

The urine was normal. There was no anemia. Complete studies of the white blood cells were not carried out, but the results of the studies that were made are recorded in table 2 and in figure 2. The Wassermann reaction of the blood was negative. The sedimentation rate was 24 mm. in forty-five minutes and 25 mm. in sixty minutes. Blood cultures and agglutination tests for *B. typhosus*, *Br. abortus* and *Brucella melitensis* gave negative results. The cerebrospinal fluid obtained on the sixth day was normal. The Friedman test for pregnancy was positive.

The onset of a short biphasic high fever preceded by a rash, ushered in with prostrating pains, terminating with intractable itching, accompanied by glandular enlargement and leukopenia and resulting in an abortion all suggest the classic picture of dengue.

CASE 7.—A. B. C., a 35 years old garage worker, married, was interviewed six days after his illness through the courtesy of Dr. J. M. Read, who had made a tentative diagnosis of "breakbone fever" as he was familiar with the findings in the first five cases reported. The patient had been camping out at Dardanelles in Tuolumne County, Calif., and while he was riding through the brush a tick had entered the left leg. Six days later, after his return to San Francisco, he noted marked aching in the hips and "on each side of the backbone." For the next two days he had terrifically severe aching in the sacro-iliac region and in that of the hip and also in the upper portion of the legs and in the back and shoulders. He had had grip and said the present pain was far worse than anything he had experienced previously. He also had pain in the testicles "as if they were continually being squeezed." He recalled no other outstanding symptoms and had not taken his temperature. He felt much better on the fourth day and was free from pain, but he grew feverish on the fifth day and then called in Dr. Read. The temperature at that time was 103 F., and the patient was prostrated. The temperature was lower on the sixth day, and steady improvement occurred thereafter although the patient stated that his body still felt tired all over as if he had just walked many miles.

The type and distribution of the pains, particularly the testicular involvement, the division of the illness into two distinct episodes with a high fever and the lack of respiratory symptoms suggest the clinical picture of a relatively mild attack of dengue. Although the occurrence of a tick-bite fever has been reported in California, the disease is not known to occur in Tuolumne County, and it is usually associated with the typical petechial rash.

CASE 8.—J. W. C., a 26 year old physician, single, who worked in a pathologic laboratory, became ill on July 22, 1934. His past history was not unusual except for the fact that he had suffered with chronic sinusitis for years. He had not been out of San Francisco during the summer. He was troubled a good deal by flea bites. The first day of his illness he suffered from general malaise and had a slight

cough. The next day he had some aching and felt ill but kept at work. That evening the temperature was 101 F. He was prostrated for the next two days and suffered from extremely severe generalized aching from head to foot, including the limbs. The temperature reached 104 F. each day. The patient was admitted to the hospital at noon on the fourth day of the illness. Physical examination revealed no evidence of infection of the respiratory tract and showed nothing to account for the fever. The inguinal lymph glands were moderately enlarged. The next morning the temperature fell to normal and remarkable improvement seemed to have occurred. The temperature rose again that evening, and on the sixth and seventh days it varied between 100 and 104 F., returning to normal on the eighth day. During this exacerbation of the fever the spleen was readily palpable and scattered râles developed in the chest. The patient did not cough or feel particularly ill, but he suffered from such intense generalized itching that he could not sleep. The râles in the chest increased on the eighth day, and on the ninth day roentgenograms showed a small area of grayness in the middle field of the right lung despite the fact that the patient seemed quite well clinically. Two days later the râles had cleared and the roentgenogram showed that the lung was nearly normal. During the illness the pulse rate ranged from 84 to 128 and the respiratory rate from 18 to 24.

The urine and sputum were normal. Culture of the blood gave negative results. The red cells numbered 4,665,000, and the hemoglobin was 93 per cent. The total leukocyte counts fell within the normal range and are recorded in table 2.

The hospital record of this patient was made available through the courtesy of his physicians, Dr. A. Stockton and Dr. D. Hines. A diagnosis of dengue was suggested by Dr. W. Dock, who saw the patient in consultation and who was familiar with the previous reports. The clinical course of the disease is in keeping with that of the manifestations in the previous cases as it showed a self-limited fever lasting eight days with generalized aching at the onset and pronounced pruritus in the latter part of the illness. Respiratory disturbances were not noteworthy until after improvement set in. There was definite splenomegaly, and leukocytosis did not occur.

CASE 9.—A. K., a 19 year old schoolboy, was seen during his illness at the hospital through the courtesy of his physicians, Dr. E. Olsen and Dr. E. B. Shaw. His previous history was irrelevant except for the fact that he had been troubled much by flea bites shortly before his illness and there had been mosquitoes in the house, although he did not recall having been bitten. The afternoon before admission to the hospital there developed "at 4 o'clock in the afternoon" a severe frontal and occipital headache and backache; the eyes ached and were sensitive to light. The next day there was a high fever, and the patient was prostrated and seemed ill. His physician thought that the neck was slightly stiff, but he found no other abnormalities on physical examination. He suspected that the patient might have poliomyelitis and sent him to an isolation hospital for lumbar puncture and observation. The temperature on entry was 103.4 F. There was marked photophobia. The next day the aching stopped; the eyes ached less, and the temperature dropped to normal. The fever returned on the following day, the fourth day of the illness, and a faintly pink maculopapular rash developed over the chest, abdomen, back and thighs. All the subcutaneous lymph glands were noted to be enlarged, and the spleen was just palpable. The rash was more pronounced on the fifth day; on

the sixth day it disappeared, the fever ceased and the patient seemed quite well again. The course of the fever from the second day on is shown in figure 7. The pulse rate was increased in proportion to the temperature. The respiratory rate varied between 20 and 22.

Examination of the urine showed nothing unusual. The hemoglobin was 100 per cent. The white cell counts showed leukopenia. The results of the counts are shown in table 2 and in figure 2. The sedimentation rate was 20 mm. in three hours. The Wassermann reaction of the blood was negative. Agglutination tests for *Brucella* and *Bact. tularensis* were negative. The cerebrospinal fluid was clear. The pressure was 75 mm. of water. The Pandy and Nonne tests were negative.

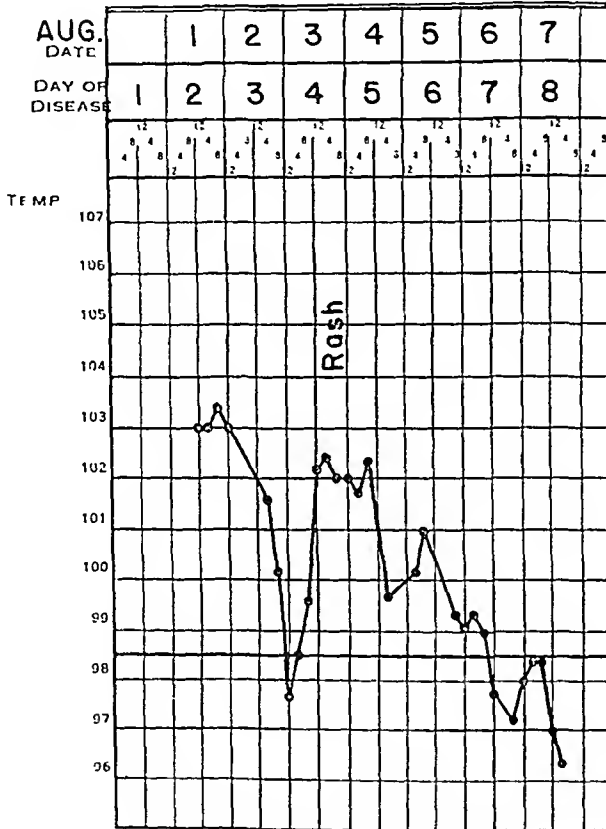


Fig. 7 (case 9).—Curve for temperature, showing the characteristic biphasic form of seven day fever.

There were 2 lymphocytes per cubic millimeter of fluid. The sugar content was normal. Cultures of the fluid were negative. A Weil-Felix agglutination test was negative.

The sudden onset of severe headache, backache and photophobia, the biphasic temperature lasting six days, the late rash, the enlargement of the lymph glands and spleen and the leukopenia in the absence of involvement of the respiratory tract make up an almost complete picture of dengue.

CASE 10.—J. D. J., a 26 year old housewife, was first seen on Aug. 29, 1934. She complained of weakness, persistent vomiting and jaundice. Extensive psoriasis

had been present since childhood. She had been married three and one-half years and had three children living and well; the youngest was 3 months of age. She was a trained nurse and was known to have been anemic for four or five years, the hemoglobin content of the blood varying between 50 and 60 per cent. She had menorrhagia due to small fibroids and had been underweight since the birth of her first child. No mosquitoes were observed about her home, and she did not suffer from flea bites, although all her children were badly bitten. Her husband had been brought home from work out of town suffering from high fever, prostration and jaundice. He was up and about but was still weak and yellow when she became ill.

On August 19, ten days before she first came under medical observation, she suddenly grew sick, with high fever, aching and prostration. The temperature was 104 F. for three days, and severe headache and backache were present. The patient complained of "the worst pain in the sacro-iliac regions." The limbs ached less severely, but there were pain and stiffness in "all the joints" although no swelling was noted. There was no coryza, sore throat or cough. The patient was so ill that she did not know whether there was a rash or not or whether she had conjunctivitis. On the fourth day all the painful symptoms were relieved, and the temperature returned to normal. However, there developed persistent vomiting, anorexia, a taste in the mouth "like a bird cage" and constipation. The temperature rose again on the fifth day and varied between 101 F. and normal for the next three days. There had been only a slight rise in the afternoon for the previous two days, but on the ninth day the patient first noted a definite yellow color of the eyes and skin.

Physical examination revealed a young woman much underweight, anemic and jaundiced. The scleras were yellow. The pupils responded normally to light. The tongue was covered with a light tan coating. The teeth were in good condition, and the gums and pharynx appeared free from inflammation. The heart and lungs were not remarkable. The blood pressure was 122 systolic and 78 diastolic. Abdominal examination showed the liver to be enlarged 1 fingerbreadth below the right costal margin and exquisitely tender. The spleen was not palpable, and splenic dulness was not increased. The knee jerks and ankle jerks were lively and equal. Small glands could readily be palpated in the left cervical region; the patient had noted early in her illness that the glands were enlarged both in the axillae and in the groins. The skin showed old lesions of psoriasis. The temperature was 99 F., and the pulse rate, 80.

The urine was normal. The blood count showed 3,300,000 red cells and 60 per cent hemoglobin. Leukopenia was present, the details of which are recorded in table 2. The sedimentation rate was 9 mm. in forty minutes and 13 mm. in one hour. The icteric index was 25 units.

Six days later the patient was seen again, and there was much improvement. There had been no further vomiting and no fever. The liver was not palpable, and there was only slight tenderness at the right costal margin. The icterus had almost cleared up. The icteric index was 14 units. Ten days later the patient felt well and was no longer jaundiced, but the icteric index was 12.5 units.

Note on Illness of Patient's Husband.—It was not possible to interview this patient's husband, but she gave the following facts about his illness: On August 11 he returned home from a week's trip on a boat. He had sailed from San Francisco to Seattle and returned. Before that trip he had not been out of San Francisco for several months. The last three or four days on the boat he was acutely ill. The fever was high and there was generalized aching. He was ill at home for three or four days, and then jaundice and soreness in the right side

developed. This occurred about the eighth day of his illness and about four days before Mrs. J. D. J. became ill.

This young woman gave a clear history of high fever with headache and marked generalized aching followed by severe vomiting and jaundice. She was found to have generalized adenopathy, tenderness of the liver and leukopenia. The jaundice cleared quickly. These findings following the occurrence of a similar illness in her husband are suggestive of dengue with hepatitis and are similar to the disturbances exhibited by two of the patients in whom the disease was produced by inoculation. The illness seemed too acute and the jaundice too brief to be characteristic of the ordinary catarrhal jaundice.

COMMENT

As the findings in these ten cases are so like those seen in cases of dengue in most respects, the diagnosis of this disease must be carefully considered.

The following points are important in considering a diagnosis of dengue:

1. The clinical picture is characteristic but may be closely simulated by several other conditions. It has been adequately described by a number of authors, including Siler, Hall and Hitchens.² They worked in the Philippines and in 1926 published a valuable monograph. This picture may be presented most concisely by quoting from them:

Typical cases are characterized by sudden onset with physical weakness, headache, postorbital pain and soreness, flushing of the face, suffusion of the eyes, anorexia with loss of the sense of taste, backache, pain in the bones and joints, marked prostration, mental depression, and a general feeling of wretchedness. There is a secondary or terminal eruption of a polymorphous character.

2. There is a short period of high biphasic fever averaging less than a week; the fever is not associated with leukocytosis and is usually accompanied by pronounced leukopenia.

3. The presence of such a disease in epidemic form is highly characteristic, as it affects a community more completely than nearly any other infection. Endemic cases occur in an area in which epidemics prevail and consequently are readily recognized.

4. There must be present a vector capable of transmitting the disease.

5. The disease can be experimentally produced in primates³ by injections of whole blood or of serum even after it has been passed

2. Siler, J. F.; Hall, M. W., and Hitchens, A. P.: *Dengue Fever: Its History, Epidemiology, Mechanism of Transmission, Etiology, Clinical Manifestations, Immunity and Prevention*, Philippine J. Sc. **29**:1, 1926.

3. Simmons, J. S.: *Dengue Fever*, Am. J. Trop. Med. **11**:77, 1931.

through a Berkefeld filter. Direct inoculation with blood produced the disease in practically 100 per cent of nonimmune persons. The inoculation of certain races of monkeys⁴ may give positive results, but no other laboratory animals are susceptible to the disease, although the virus may appear in the blood of guinea-pigs without producing any clinical manifestations.⁵ All methods of culturing the virus are discredited at present.

The symptoms and signs observed in this small series of ten cases conform closely to those described in detail by the Philippine authors who emphasized that the symptomatology of dengue may be more extensive and variegated than the usual description found in textbooks suggests. This is well illustrated by the division of cases in the epidemic which prevailed in Athens, Greece, in 1928 into seven groups. Four hundred thousand cases occurred, and Bensis⁶ described cases in which hyperpyrexia, rheumatic and hemorrhagic symptoms and disturbances of the gastro-intestinal tract, heart, adrenal glands and nervous system were noted. An adequate idea of the polymorphism of dengue can best be obtained by reading the original description of various widely separated epidemics.⁷

Only certain findings characteristic and distinctive of dengue which seem to have their counterpart in the manifestations observed in the local cases will be discussed. Severe pain is a dominant feature, and because of the intensity of the pain in the back and limbs the disease is widely known as break-bone fever. The pain is often most excruciating in the sacro-iliac region and may involve a certain area, such as a shin

4. Dinger, J. E., and Snijders, E. P.: Relation of Dengue to Development of Immunity Against Yellow Fever: Experimental Studies, Arch. f. Schiffs- u. Tropen.-Hyg. **35**:497, 1931.

5. Blanc, G.; Caminopetros, J., and Manoussakis, E.: Quelques recherches expérimentales sur la dengue, Bull. Soc. path. exot. **21**:525, 1928.

6. Bensis, W.: Etude clinique de la dengue, Paris méd. **2**:137, 1931.

7. (a) Rush, B.: Medical Inquiries and Observations: An Account of the Bilious Remitting Fever, as it Appeared in Philadelphia in the Summer and Autumn of the Year, 1780, Philadelphia, Prichard & Hall, 1789. (b) Dickson, S. H.: On Dengue: Its History, Pathology and Treatment, Philadelphia, Haswell, Barrington & Haswell, 1839. (c) Nothnagel, C. W. H.: Encyclopedia of Practical Medicine, Philadelphia, W. B. Saunders Company, 1910, vol. 10, p. 719. (d) Cleland, J. B.; Bradley, B., and McDonald, W.: Dengue Fever in Australia: Its History and Clinical Course, Its Experimental Transmission by *Stegomyia Fasciata*, and the Results of Inoculation and Other Experiments, J. Hyg. **16**:317, 1917. (e) King, W. W.: Epidemic of Dengue in Porto Rico, 1915, New Orleans M. & S. J. **69**:564, 1917. (f) Lane, F. F.: A Clinical Study of 100 Cases of Dengue at St. Thomas, V. I., U. S. Nav. M. Bull. **12**:615, 1918. (g) Rice, L.: A Clinical Report of the Galveston Epidemic of 1922, Am. J. Trop. Med. **3**:73, 1923. (h) Scott, L. C.: Dengue Fever in Louisiana, J. A. M. A. **80**:387 (Feb. 10) 1923. (i) Siler et al.² (j) Bensis.⁶

or a shoulder blade, with greater intensity than any other part. A headache may be the most pronounced pain and may be generalized or limited to the occipital or frontal regions or to both. Arthritis of one or more joints is occasionally the outstanding complaint. Table 1 shows that severe backache was present in 100 per cent of the local cases and pain in the limbs in 90 per cent. Severe headache was also present in 90 per cent, and stiffness of the joints was complained of in 70 per cent. The description of the symptoms in case 1 gives a graphic picture of the pain and suffering that the patient experienced; the symptoms led to the suspicion that he might be suffering from dengue. In all the cases the pain and aching were out of proportion to those which commonly accompany grip and influenza and many other febrile disturbances and were actually prostrating. This is well illustrated by the words of the Japanese patient (case 6) who "could not move from the neck down."

A number of patients have a typical appearance which in itself suggests a diagnosis of dengue but may be missed if the patient is not observed early in the illness. Although this was noted in only three of the cases in the present series, it is so striking that it deserves special attention. The deeply flushed head and neck of the patient suggest that he has just emerged from an overlong stay in a Turkish bath. The eyes are puffy and bloodshot and resemble those of a mastiff. Conjunctivitis and photophobia may be extreme and recall the appearance of many children with measles. Pain back of the eyeballs is constant, and the eyeballs are tender to pressure and are often fixed, as it causes pain to move them. Such a facies has been likened to the appearance of some one who has been on a drunken debauch. An unusual disturbance in vision for color may occur, which in the absence of poisoning from *santonin* and a few other drugs has apparently been described only in cases of dengue. The patient sees flashes of yellow light which appear and disappear rapidly. Such a visual phenomenon was disturbing to I. A. (case 1). The possible significance of this xanthopsia was lost until it was discovered that many of the patients with dengue studied in the Philippines had the same symptoms.

Another bizarre disturbance of sensation is the loss or the perversion of the sense of taste. This is a well recognized symptom in cases of dengue and is distinct from the loss of appetite which occurs commonly in attacks of most types of fever. It was present in four of the first five local cases and in case 10. Taste was completely lost in two cases, and in the other three the patients stated that all food tasted the same. To two of these patients everything tasted dead or putrid, and to the other even sugar tasted sour.

Gastro-intestinal disturbances are a striking feature of some epidemics of dengue and at times have led to unnecessary laparotomy.⁶

They have been of minor incidence in other outbreaks.⁸ The tongue usually shows a thick creamy coating. Vomiting and pain in the upper part of the abdomen may be marked. The vomitus is clear or bile-stained but is not "black" as in cases of yellow fever. The gastric pains and distress are said to be due to an "enantherma" of the gastric mucosa comparable to the rash on the skin.⁶ Constipation is common, and in some cases diarrhea is present and may be severe. Gastro-intestinal disturbances were conspicuous in only two of the cases observed (cases 1 and 10).

Symptoms of involvement of the respiratory tract are noteworthy only on account of their frequent absence. Sore throat, bronchitis or complicating pneumonia occurs rarely in cases of dengue, although marked reddening of the pharynx is not uncommon. A condition called "pleurodynia"⁹ is possibly a form of dengue, and pains in the chest and pleurisy are a feature of that disease. However, râles in the chest with slight cough were present in four of the first five local cases and in case 8. These signs appeared late in the disease and were usually most marked when the fever had subsided and much improvement had occurred. The râles were coarse and moist, were heard at the base of one or both lungs, shifted frequently and were unaccompanied by any other unusual signs except perhaps the slight dulness noted in case 8. In this case a definite shadow in the roentgenogram of the right pulmonary field appeared after the fever subsided and cleared quickly, showing that more than a bronchitis was present. Unfortunately no roentgenograms were made in the other cases.

The cutaneous manifestations of rash and severe itching are of great diagnostic value. The rash has been well described by Rice^{7j} and occurs at two stages of the infection. There is an initial evanescent mottling, which is often missed, so that its frequency is difficult to determine and its importance is slight. The more characteristic cutaneous eruption usually occurs during the second stage of the fever or appears terminally and is responsible for the names "spotted fever" and "giraffe fever." It may assume a variety of forms and is often macular or scarlatiniform. In some epidemics it is present in 80 per cent of the cases.¹⁰ Osler stated that it is present in only 40 per cent of the cases.¹¹ Rush,^{7a} in the first description of dengue in the United States, written in 1789,

8. Siler et al.² Lane.^{7f}

9. Dabney, W. C.: Account of an Epidemic Resembling Dengue Which Occurred in and Around Charlottesville and the University of Virginia in June 1888, *Am. J. M. Sc.* **96**:488, 1888. Torrey, R. G.: Epidemic Diaphragmatic Pleurodynia or "Devil's Grip," *Am. J. M. Sc.* **168**:564, 1924.

10. Siler et al.² King.^{7e}

11. McCrea, T., in Osler, W.: *Modern Medicine, Its Theory and Practice*, Philadelphia, Lea & Febiger, 1925, vol. 2, p. 1420.

hardly mentioned it, but Dickson^{7b} in 1839 considered it an essential part of the symptomatology. Table 1 shows that an initial rash was noted in only one of the seven cases observed and that a late rash appearing in a late stage was present in 30 per cent of the cases in this series.

Pruritus may be intense and often precedes the appearance of the secondary rash, and in a number of cases it is apparently substituted for the latter as no discoloration of the skin occurs. When this severe itching is present it is an outstandingly distressing manifestation and is highly suggestive of dengue, as it has not been described as a feature of other short febrile disorders. It was present in cases 1, 3, 4 and 8. In three of these cases scratching could not be controlled for two or three days.

Two of eight male patients (cases 1 and 7) complained of pain and some tenderness in the testicles, a symptom which has been said to be common in cases of dengue.² It may be in keeping with general aching in other parts of the body, but Nicolas¹² has reported a group of five cases with definite orchitis. A generalized moderate enlargement of the lymph glands is frequently observed and was noted in three of the cases produced by inoculation and in cases 6, 9 and 10 of this series. It may have been present in case 7. In case 8 the inguinal glands were large, but the patient thought they had been large for years. The latter patient and A. K. (case 9) had enlargement of the spleen, a disturbance which also occurs in dengue.^{7a}

The curve for temperature is not diagnostic of dengue but in certain respects is highly suggestive. Ordinarily there is a rapid rise in temperature followed by a short course of fever for a few days, the temperature often dropping to normal or subnormal at about the middle of the febrile period, and a more or less abrupt termination. The names "three day fever," "five day fever" and "seven day fever" best illustrate the brevity of the pyrexia. The characteristic diphasic or saddleback fever is often lacking in epidemic cases and is more frequently encountered in cases produced by inoculation.¹³ The temperature commonly reaches 102 or 103 F. and may reach 105 F. or over.¹⁴ There may be slight rises after the acute illness has terminated. Various forms of curves for temperature have been described by Rice^{7c} in his report on the epidemic which occurred in Texas in 1922.

The curves for temperature for cases 1, 2 and 9, (figs. 1, 3 and 7) may be taken as excellent examples of the course of fever in dengue, as

12. Nicolas, C.: Six cas d'orchite ou ovarite, complications de la dengue, *Bull. Soc. path. exot.* **20**:402, 1927.

13. Siler et al.² Simmons.³

14. Watson, M.: A Case of Dengue Fever with Hyperpyrexia, *J. Trop. Med.* **36**:157, 1933.

they conform so closely to the usual description and vary from those for other forms of fever usually encountered. Two paroxysms of fever could be readily recognized in 60 per cent of the cases, although the interval of low temperature was relatively short, lasting for a number of hours rather than for days. The curve in case 5 (fig. 6), one of the cases produced by inoculation, was the only one which is unlike the usual picture, but the complicating factor of hepatitis may be responsible. The temperature reached 103 F or over in all ten cases, and the duration varied between six and nine days, as shown in table 1. It should be emphasized that a short attack of high fever with a low white cell count should, in the absence of any obvious cause, suggest the possibility of dengue and the necessity of evaluating all the clinical findings with this diagnosis in mind.

The pulse rate in dengue may be rapid ¹¹ but has often been described as remarkably slow.⁶ In the cases reported here it varied in proportion to the intensity of the fever, and no bradycardia was evident.

The blood picture in dengue has been carefully studied by a number of observers.¹⁵ The number of red cells and the hemoglobin content are not affected. Moderate leukopenia, the count averaging from 3,500 to 5,000 white cells, is present in about three fourths of the cases and becomes most pronounced toward the termination of the illness. The leukocyte count may be unaltered, and at times there is slight leukocytosis in early stages of the disease.¹⁶ When there is leukopenia the diminution of cells affects the polymorphonuclear leukocytes, producing a relative increase in the proportion of the mononuclear cells. The young forms of polymorphonuclears are increased in the early stages of the infection, producing a characteristic shift to the left in the Schilling count, and Catsaras¹⁷ has reported marked degenerative changes in the older cells; he expressed the belief that this is direct evidence of a toxic action of the virus on the leukocytes. Joannides^{15b} agreed with this theory and also noted similar changes in the large mononuclear cells, which may be increased in number.

Of the present series of ten cases, blood counts were made in nine (table 2 and fig. 2). No definite conclusions can be drawn from an analysis of such a small series, particularly as four of the patients (cases 2, 3, 5 and 8) suffered from complications which may well have

15. (a) Simmons, J. S.; St. John, J. H., and Reynolds, F. H. K.: Numerical and Morphological Alterations of Leukocytes, *Philippine J. Sc.* **44**:128, 1931. (b) Joannides, G. S.: Blood in Dengue: Morphological Examination, *Arch. Inst. Pasteur hellén* **2**:295, 1930. (c) Siler et al.² (d) Dinger and Snijders.⁴

16. Siler et al.² Dinger and Snijders.⁴

17. Catsaras, J.: Pathologisch-anatomische Beobachtungen zum Dengue Fieber, *Arch. f. Schiff- u. Tropen-Hyg.* **35**:278, 1931.

altered the white blood cell count. None of the patients became anemic. Table 2 shows that in repeated counts throughout the illness in cases 4, 6 and 9, in which there were no complications, pronounced leukopenia developed. In each a relative increase in the number of monocytes occurred as the diminution in the total number of white cells progressed. In two of these cases Schilling counts were made, and in each of the counts the percentage of early forms of polymorphonuclear neutrophils predominated over that of mature forms. The patients, then, showed the characteristic changes typical of dengue. In case 1 only two cell counts were made, and these were made on the third and fourth days of the illness. The total counts were in the normal range, but there was a marked shift to the left in the Schilling count. Regarding the cases in which complications occurred, the extreme leukocytosis in the first two patients with jaundice will be commented on further later. However, the first of these patients (case 3) had the increase in leukocytes from the third day on, together with a marked excess of neutrophils and many banded forms, while the second (case 5) had a normal number of leukocytes on the fourth and fifth days, with many immature forms, and then from the seventh day on had leukocytosis characterized by relative lymphocytosis and a Schilling count close to normal. It is difficult to explain why in one of these patients there developed a blood picture compatible with any acute infectious process and in the other there developed an extraordinary lymphocytosis. Perhaps the bronchopneumonia noted at autopsy affected the white cell count in case 3. Although the third jaundiced patient (case 10) did not come under observation until the tenth day of her illness, she showed definite leukopenia with a diminution in the number of neutrophils and a shift to the left.

The lymphocytosis that appeared in case 2 when encephalitis developed was much like that in the second case of jaundice and may represent the true reaction to the virus when it produces complications. In case 8 the blood counts on the fourth and seventh days showed a total number of leukocytes within the normal range and an increase in neutrophils, with a high percentage of banded forms. An infection of the respiratory tract which developed in a late stage of the disease was evident in this patient.

The production of the clinical picture of the inoculation type of dengue in a human volunteer by injection of blood from I. A. (case 1) may be considered the most conclusive diagnostic evidence obtained that the original patient was infected with that disease. The further transmission of the fever to other patients serves to strengthen this conclusion. Similar experiments have been carried out in widely separated medical centers, such as Manila, P. I.,¹³ Sydney, Australia,^{7a} Amster-

dam, Netherlands,⁴ London, England,¹⁸ Athens, Greece¹⁹ and Galveston, Texas,²⁰ and the same results have always been obtained. No unusual complications and no fatalities have been reported. As little as 0.00005 cc. of serum from patients with dengue injected subcutaneously²¹ has produced infection, and the amount of infective material used does not seem to alter materially the course of the disease produced. The blood is infective only during the first three or four days of the illness, and the virus remains viable when kept as long as ninety-nine hours at icebox temperature.^{7d} One observer¹⁹ has stated that the cerebrospinal fluid also contains the virus during this period, but no careful study of the spinal fluid has been reported. The virus is not present in the urine, stool or sputum. The period of incubation following inoculation may be from one to nine days but is between four and five days on the average. Table 1 shows that in cases 2 to 5 of this series the period of incubation was four days in three cases and two and one-half days in the fourth case. The average length of the illness is shown to be slightly less than eight days, which is a little longer than the average for most similar series but is in keeping with that in the six endemic cases reported.

The results of inoculating monkeys with dengue have been carefully studied.²² It need only be stated here that certain races seem to be immune and that in others the degree of infectivity is not high. Some monkeys are infected, and although they show no clinical signs of the disease, not even fever, they usually manifest definite leukopenia. Unfortunately the two monkeys which received injections of blood from L. H. (case 5) were not followed with this in mind, and clinically negative results in only two animals are of no positive value.

The fact that the results of injections of two serums into volunteers were negative may be explained in two ways: Although serum was drawn from the same whole blood which was proved to contain the virus, the longer periods of five and seven days during which it was kept in the icebox may have made it innocuous. It is also possible that the two volunteers were immune. There was no history to suggest this, but it should be borne in mind that they were both suffering from chronic encephalitis, which is due to a filtrable virus. The negative

18. Findlay, G. M.: The Relation Between Dengue and Rift Valley Fever, *Tr. Roy. Soc. Trop. Med. & Hyg.* **26**:157, 1932.

19. Manoussakis, E.: Recherches étiologiques sur la dengue, *Bull. Soc. path. exot.* **21**:200, 1928.

20. Chandler, A. C., and Rice, L.: Observations on the Etiology of Dengue Fever, *Am. J. Trop. Med.* **3**:233, 1923.

21. Koizumi, T.; Yamaguchi, K., and Tonomura, K.: A Study of Dengue Fever, *Trop. Dis. Bull.* **12**:77, 1918.

22. Siler et al.² Simmons.³ Dinger and Snijders.⁴ Blanc et al.⁵ Findlay.¹⁸

result in a volunteer with chronic arthritis who received an injection of cerebrospinal fluid from A. G. P. (case 2) is not surprising as the fluid was obtained ten days after the acute illness was over.

COMPLICATIONS

Complications and sequelae of dengue are said to be singularly uncommon. In general this is true, but a variety of forms may occur, as may be gathered from Bensis' ⁶ experiences in the extensive epidemic which prevailed in Athens, Greece. It is remarkable that four of the first five patients for whom data are given in table 1, all of whom suffered from an identical infection, had complications. The albuminuria shown by I. A. (case 1) was marked. The tremendous number of casts observed has never been encountered by me in any other febrile condition and is comparable to the urinary sediment described as occurring in yellow fever. Such a degree of albuminuria is rare in dengue but has been recorded.²³

Complications of dengue affecting the central nervous system have been noted, and they vary widely in their manifestations,²⁴ but clinical signs and changes in the cerebrospinal fluid typical of encephalitis such as those which appeared in the postfebrile stage in case 2 have not been described although Ghiannoulatos ^{24a} mentioned that encephalitis occurred in association with dengue in the epidemic in Athens, Greece. However, encephalitis is a well recognized, even if rare, complication of diseases caused by a filtrable virus, such as measles, mumps, smallpox, vaccinia, rabies and other conditions,²⁵ and a neurotropic virus of yellow fever has been isolated.²⁶ The temporary change in character, the extreme drowsiness, the dull headache with slight fever and the leukocytosis are strikingly similar to forms of epidemic encephalitis encountered over a decade ago. Lumbar puncture showed that the fluid was under increased pressure and that there was an increase in the protein content and in the number of cells. Inability to demonstrate the presence of an infective agent in the fluid by inoculation into human subjects is in keeping with the results

23. (a) Avaritsiotis, E.: Sur le neurotropisme de la dengue, *Ann. de méd.* **30**: 5, 1931. (b) Bensis.⁶

24. (a) Ghiannoulatos, G. P.: Aperçu clinique sur les séquelles nerveuses et psychiques de la dengue (Un cas de pseudo-tabes), *Rev. neurol.* **1**:599, 1931. (b) Richardson, S.: Ocular Symptoms and Complications, *Tr. Am. Ophth. Soc.* **31**: 450, 1933. (c) Avaritsiotis.^{23a}

25. Rivers, T. M.: Relation of Filtrable Viruses to Diseases of the Nervous System, *Infections of the Central Nervous System*, A. Research Nerv. & Ment. Dis. Proc. **12**:49, 1932.

26. Davis, N. C.; Lloyd, W., and Frobisher, M.: Transmission of Neurotropic Yellow Fever Virus by *Stegomyia* Mosquitoes, *J. Exper. Med.* **56**:853, 1932. Rouband, E., and Stefanopoulo, G.: Transmission of Neurotropic Yellow Fever Virus by *Stegomyia* Mosquitoes, *Bull. Soc. path. exot.* **26**:305, 1933.

of similar experiments on monkeys inoculated with cerebrospinal fluid from subjects with other forms of secondary encephalitis. Ordinarily, in the early stage of dengue, when the virus is said to be present in the spinal fluid, no pleocytosis or other changes occur, and the negative results of lumbar puncture in cases 6 and 9 are in keeping with this. Catsaras¹⁷ reported the observations made at autopsy on a patient with dengue associated with acute encephalitis.

Jaundice is said to be an uncommon complication of dengue but is well recognized. Two reports suggest that it may be frequently encountered at times. In 1923 about 29,000 cases of dengue were reported in Louisiana.^{7h} A questionnaire concerning its manifestations was sent out to all the physicians. Twenty-eight per cent of those who answered it had noted jaundice in their cases. Also in 1928 Nicolas in Northern Africa reported a small group of twenty cases of dengue, in eight of which jaundice was present.²⁷ As jaundice was noted in three cases in San Francisco (cases 3, 5 and 10) and as in each of the two produced by inoculation it appeared on the sixth day of the disease and in each of these was accompanied by a marked leukocytosis, its occurrence could hardly be a coincidence. Figure 4 also shows the degree of icterus in the three cases to be identical. As J. B. (case 3) had previously been slightly jaundiced with an attack of disease of the gallbladder it was at first thought that the reappearance of jaundice was on the same basis. The remarkable picture of hepatic necrosis noted at autopsy could hardly be unrelated to his infection. It may have occurred because the liver had been previously damaged. No report of a postmortem examination of a patient with dengue associated with jaundice can be found in the literature for comparison. This suggests that cases of "catarrhal jaundice" and acute hepatitis of unknown etiology may be due to a similar type of infection. The second patient was disturbed little by the icterus, although it was accompanied by prolonged fever and leukocytosis. The third patient was incapacitated for only a few days. No records of blood counts of patients with dengue associated with jaundice can be found in the literature to compare with the high white cell count observed in two of these cases.

DIFFERENTIAL DIAGNOSIS

The clinical findings and complications occurring in this small group of cases in San Francisco do not seem compatible with any of the conditions ordinarily encountered and are so like the picture of dengue that no differentiation from it is possible. The differential diagnosis in these cases is the same as that for sporadic cases of dengue appearing

27. Nicolas, C.: A propos d'une épidémie de dengue compliquée d'ictère: La dengue serait-elle une fièvre amarylle atténuée? *Bull. Soc. path. exot.* **21**:748, 1928.

in this locality and offers a problem far different from that which is encountered when cases occur in the tropics, in the Orient or elsewhere where the fever is common. Inoculation experiments as an aid to diagnosis are rarely feasible, so that dengue must be differentiated from a considerable number of other diseases on clinical grounds alone, and the diagnosis can usually only be presumed, and then only on the basis of exclusion of other similar conditions.

Influenza is similar in many respects. However, its usual absence in summer, when dengue occurs, the constancy of symptoms of involvement of the upper portion of the respiratory tract, the absence of generalized glandular enlargement and of rash and the more irregular course of the fever should differentiate it from dengue. Reproduction of the disorder by injections of blood into monkeys have not produced clearcut results,²⁸ and similar experiments in man have not been recorded. Severe measles in an adult may be readily confused with dengue. The presence of an epidemic, the onset with symptoms of involvement of the upper portion of the respiratory tract, the presence of Koplik spots on the buccal mucous membranes and the more extensive rash should distinguish the majority of cases, although both conditions are due to infection with a filtrable virus and measles may also be transmitted by inoculation into human subjects.²⁹ Rubella is said to occur in a severe form³⁰ with headache, conjunctivitis, photophobia, prostration and high fever and with a rash appearing several days after the onset. It was considered a possible diagnosis in case 9.

Epidemic pleurodynia has frequently been reported on the Atlantic seaboard of the United States³¹ and has been compared to dengue.^{31a} It is similar to that disease but is characterized by the outstanding complaint of pain over the lower ribs and upper portion of the abdomen and the rare presence of a friction rub. The leukocyte count may be slightly increased, or it may be low. The mode of transmission is unknown, and mosquitoes have not been proved to be the vector. It may well be a modified form of dengue.

Typhoid as a differential diagnosis may offer considerable difficulty at first. The gradual increase in temperature with the prolonged course of the fever, the absence of conjunctivitis and of pains in the joints and limbs, the dissimilarity of the rash and, above all, blood cultures positive

28. Falk, I. S.; Harrison, R. W.; McKinney, R. A., and Stuppy, G. W.: Experiments on the Etiology of the Influenza Epidemic of 1928-1929, Monographic Series, no. 11, Baltimore, American Journal of Hygiene, 1931.

29. Degkwitz, R.: The Etiology of Measles, *J. Infect. Dis.* **41**:304, 1927.

30. Schamberg, J. F., and Kolmer, J. A.: *Acute Infectious Diseases*, ed. 2, Philadelphia, Lea & Febiger, 1928, p. 567.

31. (a) Paynes, G. C.: Epidemic Transient Diaphragmatic Spasm, *J. A. M. A.* **81**:746 (Sept. 1) 1923. (b) Footnote 8.

for *B. typhosus* should make the differentiation easy when the patient is under a prolonged period of observation. In cases 1 and 6 the condition was tentatively diagnosed as typhoid. Infections with *B. abortus* may temporarily simulate dengue, but the longer course of the disease associated with positive results of blood culture and agglutination tests will establish the diagnosis. Relapsing fever at onset may give symptoms identical with those of dengue. However, the leukocytosis, the presence of spirochetes in the blood and the reproduction of the infection in mice will serve to distinguish the two. It is of interest that in cases 1 and 7 the patients were bitten by ticks; this suggests the possibility of an infection not only with spirochetes but also with the rickettsia of Rocky Mountain spotted fever. Ticks with this infection are present in Northern California,³² and all the characteristic clinical features of dengue occur in tick fever. The longer course, the hemorrhagic tendency of the rash, the slight leukocytosis with mononucleosis and the fact that the disease is readily reproduced in guinea-pigs distinguish tick fever from dengue. Typhus should be recognized on similar clinical grounds and by a positive Weil-Felix reaction. It has been reported to occur in California³³ in the mild form of Brill's disease and the Mexican tabardillo fever.

The severe headache at onset centering in the occiput and producing pain on flexing the head, the ocular signs and the fever may suggest some form of meningitis, encephalitis or even an early stage of poliomyelitis. The possibility of a meningitis was seriously considered on the sixth day in case 1, and that of poliomyelitis, on the second day in case 9. The onset of smallpox is not unlike the manifestations in dengue.

Ordinarily the natural evolution of most of the diseases mentioned will make their differentiation clear, but it may be impossible to eliminate influenza and pleurodynia and difficult to rule out severe forms of measles and rubella.

There are a large group of fevers apparently due to a filtrable virus which are at present unknown in California. Not only do they offer perplexing problems in diagnosis in the areas in which they are recognized, but the close similarity of symptomatology illustrates how difficult it is to separate clearly many of the disorders supposedly due to this type of infection. The possibility of the few cases described in Northern California belonging to this group rather than being instances of dengue itself cannot be overlooked, and a comparison of dengue with

32. Kelly, F. L.: Rocky Mountain Spotted Fever: Its Prevalence and Distribution in Modoc and Lassen Counties, California; Preliminary Report, California State J. Med. **14**:407, 1916.

33. Cumming, J. G., and Senftner, H. F.: The Prevention of Endemic Typhus in California, J. A. M. A. **69**:98 (July 14) 1917.

other clinical entities which have been confused with it will emphasize on what uncertain criteria the differential diagnosis of the whole group depends. The relationship of dengue to yellow fever is well recognized,³⁴ and mild cases of the latter cannot be distinguished from severe cases of the former disease. As a rule, jaundice, albuminuria and "black vomitus" together with a high mortality rate are characteristic of yellow fever, yet the same symptoms may occur in dengue. This is noteworthy in view of the fact that of the five cases of infection with the same strain of virus in this series, severe vomiting and albuminuria were present in one and jaundice in two. Both diseases occur in epidemics spread by the same kind of mosquito. An even closer relationship is shown by the fact that many monkeys inoculated with dengue acquire immunity to yellow fever.⁴ However, nearly all *Macacus rhesus* monkeys inoculated with the virus of yellow fever die while monkeys of the same race inoculated with the virus of dengue rarely succumb. Dinger, Schuffner, Snijders and Swellengrebel³⁵ give an enlightening discussion on the similarity of the two disorders.

A number of fevers which have been designated as "pseudodengue" or "dengue-like" have been described in different parts of the world. The seven day fever of Rogers and the five day fever of van der Scheer are now definitely thought to be identical with dengue.⁴ Papataci or sand-fly fever in Africa as described by Manson³⁶ is in no way different from dengue except that it is transmitted by a phlebotome and that a rash is not a feature. Also, a sand-fly fever is endemic in the region near Peiping, China; that disease runs a short uninterrupted course and has not been described in the literature.³⁷ The red fever occurring in the Belgian Congo may be a mild form of dengue.³⁸ The African Rift Valley fever, while clinically like dengue, is apparently due to a different virus. Monkeys immune to the virus of dengue are not immune to that of Rift Valley fever, and monkeys immunized against Rift Valley fever are susceptible to dengue.¹⁸

TRANSMISSION OF THE DISEASE

Dengue is transmitted by the bite of a mosquito. No other way of contracting the disease is recognized, and the only mosquito known

34. Dinger and Snijders.⁴ Bensis.⁶ Nicolas.²⁷

35. Dinger, J. E.; Schuffner, W. P.; Snijders, E. P., and Swellengrebel, N. H.: Untersuchungen über Gelbfieber in den Niederlanden, Zentralbl. f. Bakt. (Abt. 1) **118**:6, 1930.

36. Manson, P.: Tropical Diseases, edited by P. H. Manson-Bahr, ed. 9, New York, William Wood & Company, 1929, p. 210.

37. Meleney, H. E.: Personal communication to the author.

38. Pieraerts, G.: Red Fever of Congo May Be Dengue, Ann. Soc. belge de méd. trop. **11**:321, 1931.

to carry the virus is *Aedes Aegypti*,³⁹ as no other forms of this insect have ever been convicted except *Aedes albopictus*⁴⁰ in the Philippine Islands. Professor W. B. Herms, head of the division of entomology and parasitology at the University of California, stated that *Aedes Aegypti* does not occur in California although *Aedes varipalpus*, which closely resembles it, is endemic.⁴¹ Under these circumstances the appearance of these cases of dengue-like fever in San Francisco presupposes either that mosquitoes are now present which may transmit it or that some other vector or method of transmission is possible. During July 1934 the San Francisco Board of Health waged a campaign to clean up mosquitoes in the city as many had made their appearance during the summer. Several were killed in the home of A. K. (case 9), not far from the home of Mrs. J. D. J. (case 10). The presence of *Aedes Aegypti* has not been reported to date. The presence of these mosquitoes cannot be disregarded as offering a possible clue to the source of infection in San Francisco, and in two of the six endemic cases the patients evidently contracted the illness outside the city in areas well known to be infected with mosquitoes. Some interesting articles have appeared which stress the possibility of spreading mosquito-borne diseases by means of travel by air.⁴² In this way infected insects can be carried long distances from endemic areas in a short time. De Vilbiss, in an article entitled "Wings of Death,"⁴³ has described the precautions taken by the United States Public Health Service to prevent such an occurrence. Only a long series of carefully controlled experiments or the appearance of an epidemic of dengue can settle the point as to whether or not infected mosquitoes are present in San Francisco.

As it has been pointed out that yellow fever, which has always been thought to be transmitted by mosquitoes alone, has been transmitted by ticks in Brazil,⁴⁴ and as two of the patients of this series were bitten by ticks shortly before the onset of the fever, the possibility of this vector's being the infecting agent must be considered. However, as none of the other patients had been outside of San Francisco shortly before becoming ill, and as ticks do not naturally occur in the city, it is hard to see

39. Snijders, E. P.; Dinger, E. J., and Schuffner, W. P.: On the Transmission of Dengue in Sumatra, *Am. J. Trop. Med.* **11**:171, 1931. Siler et al.² Simmons.³

40. Simmons, J. S.; St. John, J. H., and Reynolds, F. H. K.: Dengue Fever Transmitted by *Aedes Albopictus* Skuse, *Am. J. Trop. Med.* **10**:17, 1930.

41. Herms, W. B.: Personal communication to the author.

42. Cullen, J. P.: Dengue Fever, *J. Trop. Med.* **35**:289, 1932. Legendre, J.: Transmission of Dengue by Land and Sea Routes, *Presse méd.* **41**:1261, 1933.

43. De Vilbiss, L. A.: Wings of Death (Spread of Mosquitoes by Airplane), *Hygeia* **11**:902 (Oct.) 1933.

44. de Beaurepaire Aragao, H.: Transmission de la fièvre jaune par les tiques. *Compt. rend. Soc. de biol.* **114**:137, 1933.

how these patients could have been infected in that manner, unless the disease was acquired through contact with dogs harboring the parasites.

Sand-fly fever occurs in such widely separated areas as Peiping, China, and Northern Africa,⁴⁵ and the disease clinically is so much like dengue⁴⁶ that a phlebotome may be considered as a vector. There is no evidence that this method of transmission is possible in Northern California. The majority of the patients had suffered from flea bites, but fleas are so common in San Francisco that no real significance can be attached to this. However, if fleas can transmit plague and typhus they may carry other types of infection. There is nothing in the history of the cases to suggest that the louse was a vector.

CONCLUSIONS

Six cases of high, usually biphasic, fever averaging a week in duration and not accompanied by symptoms of involvement of the upper portion of the respiratory tract or leukocytosis were observed in San Francisco during the summer of 1934. They appear to represent a disease entity new in Northern California. The clinical findings in these six cases and in four other cases produced by inoculation with whole blood are practically identical with those of dengue. The incidence of complications was higher than is usual in dengue, but their nature is the same. This may be explained on the ground that the local population is less resistant to this type of infection.

However, as dengue commonly makes its appearance in a new field in the form of a widespread epidemic and as the only known vector is the mosquito *Aedes Aegypti*, which has never been observed in California, the disease in these cases cannot positively be diagnosed as dengue. Also, it has not been shown that the infective agent in these cases was truly a filtrable virus, and it has not been possible to show whether an immunity to dengue developed after the attack. Under these circumstances it seems wisest at present to classify this type of febrile disorder as "dengue-like," although all the clinical evidence points toward its being dengue. It is hoped that if this fever recurs next summer its exact status may be accurately determined.

45. Manson-Bahr.³⁶ Meleney.³⁷

46. Megaw, J. W. D.: Dengue-Sand-Fly Fever Problem, *Indian M. Gaz.* **58**: 401, 1923.

HYPERGLYCEMIA AND GLYCOSURIA ASSOCIATED WITH DISEASE OF THE BILIARY TRACT

HERMAN LANDE, M.D.
AND
HERBERT POLLACK, M.D.
NEW YORK

The intimate relationship of disease of the biliary tract to pancreatitis and its significance as an etiologic factor in the production of glycosuria and diabetes mellitus are generally recognized. Joslin¹ stated that cholelithiasis is one of the important etiologic factors in cases of diabetes of adults. He emphasized the importance of eradicating disease of the gallbladder in this type of diabetes and cited several cases that demonstrated the favorable influence of this procedure on sugar tolerance.

Cambridge² in a letter to the editor of the *Lancet* commented:

It has long been recognized that glycosuria is a relatively uncommon result of the chronic interstitial pancreatitis associated with gall-stones, and that when it does occur it is of a mild type. But the disease is usually progressive and, although operative interference may bring about an improvement in the patient's carbohydrate tolerance, it is only temporary and frank diabetes ultimately results.

Smithies,³ in a commentary on a paper by Barber, stated:

So-called diabetes with gall tract disease is not a true diabetes. Glycosuria appears in from three to six per cent of these patients. The glycosuria results from indirect interference with island function consequent upon pancreatitis, and from faulty glycogen storage as a result of hepatitis. Treatment of the biliary tract diseases by non-surgical drainage or in selected instances by surgery markedly affects the glycosuria.

Lichty and Woods⁴ in 1925 in an analysis of 23,464 patients found 1,474 cases of disease of the gallbladder and biliary tract, 455 cases of glycosuria and 25 cases of disease of the biliary tract with glycosuria. They reported 3 cases of diabetes mellitus apparently cured by operation on the gallbladder.

From the surgical wards of the Mount Sinai Hospital.

1. Joslin, E. P.: *Treatment of Diabetes Mellitus*, Philadelphia, Lea & Febiger, 1928.

2. Cambridge, P. J.: *Lancet* 1:846, 1927.

3. Smithies, F., in discussion on Barber, W. H.: Cholecystitis and Its Relation to Pancreatitis, *J. A. M. A.* 87:1635 (Nov. 13) 1926.

4. Lichty, J. A., and Woods, J.: *Am. J. M. Sc.* 167:1, 1924.

As long ago as 1907 Hochhaus⁵ reported 2 cases of cholelithiasis with an increased severity of the associated diabetes during the acute attack. The subsidence of disease of the gallbladder was accompanied by a marked improvement in the sugar tolerance.

Rabinowitch and Bazin⁶ reported several cases of disease of the gallbladder complicated by hyperglycemia. They published the dextrose tolerance curves for these patients before and after surgical procedure. The protocols presented are incomplete, but there is no doubt that in some of their patients there was a restoration of normal tolerance for dextrose. The authors' evidence for attributing the impaired tolerance for dextrose to chronic pancreatitis seems inadequate. Eustis⁷ stated: "It is well known that after diabetes is established there is no cure and efforts are only palliative." He reported a series of 36 cases of so-called alimentary glycosuria. In 15 of these, or 41.6 per cent, there was definite disease of the gallbladder, and in 6 of the latter group true diabetes with hyperglycemia developed. Silverman,⁸ in commenting on Eustis' observation, reported 30 cases of chronic pancreatitis secondary to disease of the gallbladder. He did not find diabetes in any patient of this series.

Kohn⁹ mentioned the cases of 3 patients in whom diabetes developed while the patients were being treated for disease of the gallbladder. Two patients showed considerable improvement in their carbohydrate tolerance following operation. The third improved after duodenobiliary drainage.

Shapland¹⁰ reported a case of diabetes complicated by gallstones. The diabetic symptoms preceded the symptoms of cholelithiasis by at least two years. The duration of the diabetes was eight years. Surgical removal of the gallbladder resulted in improved tolerance for carbohydrates.

Baker and Ryneerson¹¹ have recently reported improvement in the diabetic status following cholecystectomy in 2 patients, in 1 of whom definite hepatitis was noted on gross examination.

Himsworth¹² reported the case of a patient under care for a condition of the liver requiring surgical intervention. There was no previous history of diabetes, but on admission to the hospital a trace of sugar

5. Hochhaus: *Deutsche med. Wchnschr.* **33**:1677 (Oct. 10) 1907.

6. Rabinowitch, I. M., and Bazin, A. T.: *Ann. Surg.* **94**:354, 1931.

7. Eustis, A.: *New Orleans M. & S. J.* **75**:449, 1923.

8. Silverman, D. N.: *New Orleans M. & S. J.* **75**:592, 1923.

9. Kohn, L. W.: *New York State J. Med.* **26**:182, 1926.

10. Shapland, C. D.: *Lancet* **1**:758, 1927.

11. Baker, T. W., and Ryneerson, E. H.: *Proc. Staff Meet., Mayo Clin.* **9**:81, 1934.

12. Himsworth, H. P.: *Clin. Sc.* **1**:1, 1933.

was found in the urine. Under observation this condition became worse, until 140 units of insulin was given without controlling the glycosuria and ketonuria. Autopsy revealed the bile ducts throughout the liver to be blocked with gallstones and the liver grossly damaged. The pancreas was normal.

The association of the disease of the biliary tract and diabetes has been definitely established, but the nature of the underlying disturbance of carbohydrate metabolism remains obscure. Ever since Opie¹³ demonstrated the relationship of cholelithiasis to disease of the pancreas it has been assumed that the glycosuria is a manifestation of the associated pancreatitis. Warren¹⁴ pointed out the tendency to relate complacently almost any type of pancreatic lesion to diabetes without much regard to changes seen in the pancreas of nondiabetic persons. Any lesion found in the pancreas of a diabetic person which involves either the island tissue or the acinar tissue, or both, can be duplicated in the pancreas of a nondiabetic person. The acceptance of the interstitial pancreatitis of disease of the gallbladder as a complete explanation of the disturbance of carbohydrate metabolism fails to consider the much greater frequency with which this same pathologic condition is not associated with either hyperglycemia or glycosuria.

The evidence that the improvement in the diabetic status following biliary drainage is due to the removal of a focus of infection is not entirely convincing. There was no definite evidence of infection in several of the cases reported. Furthermore, there is no such striking improvement following the removal of a similar focus elsewhere in the body.

The possible hepatic origin of glycosuria and hyperglycemia has been suggested, a theory supported by the extensive damage to the liver often encountered in cases of disease of the biliary tract.

REPORT OF CASES

CASE 1.—A man aged 63 years was admitted to the hospital on Feb. 21, 1934. Eight months before he had had an appendectomy, at which time glycosuria was not noted. For one month before admission to the hospital there had been intermittent nonradiating colicky pains in the epigastrium. There had been an acholic stool five days, and another one day, before admission to the hospital. When the patient was first seen there was slight jaundice. The edge of the liver was palpable 3 cm. below the costal margin. Definite tenderness was elicited in the right upper quadrant of the abdomen. The systolic blood pressure was 130 mm. of mercury and the diastolic 78 mm. Physical examination otherwise gave essentially negative results. The stools were light gray. The urine contained 2 per cent sugar but no acetone. The concentration of cholesterol was 250 mg. and that

13. Opie, E. J.: *Diseases of the Pancreas*, Philadelphia, Lea & Febiger, 1926.

14. Warren, Shields: *The Pathology of Diabetes Mellitus*, Philadelphia, Lea & Febiger, 1930.

of the sugar, 185 mg., per hundred cubic centimeters of blood. The icteric index was 40 units. The urine became sugar-free in two days and remained so with a diet of 160 Gm. of carbohydrate, 70 Gm. of protein and 80 Gm. of fat with 45 units of insulin daily.

On March 6 a cholecystectomy was performed, and the common duct was drained through the stump of the cystic duct. A number of small faceted stones were removed. Subsequent analysis showed these to be composed of cholesterol and calcium bilirubinate. For one week postoperatively the patient had a low grade fever owing to infection of the wound caused by *Bacillus pyocyaneus*. Because of nausea he was unable to tolerate even a soft diet.

On March 8 the patient was given a regimen of alternate two hour feedings of 8 ounces (236 cc.) of milk and 8 ounces of orange juice with respective doses of insulin of 5 and 10 units. On March 10, because the urine contained from 2.5 to 4 per cent sugar, the doses of insulin were increased to 10 and 15 units, respectively, with the feedings kept as already mentioned. In the course of the next twenty-four hours the patient was given 40 ounces (1,180 cc.) of orange juice and 32 ounces (944 cc.) of milk, with 100 units of insulin, and at the end of this time the urine was free from sugar. On March 11 the dosage of insulin was sharply reduced. At 10 a. m. 10 units of insulin was given with 8 ounces of orange juice, at 2 p. m., 5 units of insulin with 8 ounces of milk, and at 6 p. m., 5 units of insulin with 8 ounces of milk. At 6:30 the patient suddenly became stuporous and could not be aroused. His eyes were set and glassy, the pupils did not react, and the pulse was weak and irregular. There were urinary and fecal incontinence and generalized twitchings, during which time the blood pressure rose to 210 systolic and 120 diastolic. Because of the difficulty encountered in trying to inject dextrose intravenously this episode lasted three fourths of an hour. There was prompt recovery after the intravenous injection of 15 cc. of 50 per cent dextrose. The patient was then able to swallow 8 ounces of orange juice. On the following day he was given a diet of 150 Gm. of carbohydrate, 70 Gm. of protein and 80 Gm. of fat with 30 units of insulin. After twenty-four hours the urine was sugar-free. On March 20 the urine was sugar-free with the same diet but with no insulin. On March 29 the urine was sugar-free with 200 Gm. of carbohydrate, 70 Gm. of protein and 80 Gm. of fat with no insulin. At this time the blood sugar after fasting was 120 mg., and the icteric index, 10. On April 4 readings for dextrose tolerance were:

Time	Blood Sugar, Mg. per 100 Cc.
9:05 (after fasting).....	65
(100 Gm. dextrose at 9:15)	
9:45	96
10:15	141
11:15	118
12:15	92

CASE 2.—A man aged 60 was admitted to the hospital on Feb. 22, 1934. There had been a sudden onset four weeks before his admission to the hospital with nausea and vomiting. Increasing jaundice developed, associated with moderate pruritus, acholic stools and very dark urine. The jaundice became progressively more intense. There was a loss of 14 pounds (6.4 Kg.) in four weeks. During this period there developed increasing thirst and polyuria. Urinalysis one week before admission to the hospital revealed the presence of sugar. On admission there was intense icterus and the edge of the liver was palpable 3 cm. below the costal margin. There was an enlarged, firm spleen. A provisional diagnosis was

made of biliary obstruction due to carcinoma of the head of the pancreas. The stool was acholic, and the urine contained 4.4 per cent of sugar. The total blood cholesterol was 1,165 mg. per hundred cubic centimeters, 750 mg. of this amount being in the form of esters. The icteric index was 105; the blood urea was 16 mg., and the blood sugar, 115 mg., per hundred cubic centimeters. The patient was given a diet of 200 Gm. of carbohydrate, 60 Gm. of protein and 40 Gm. of fat. At first it was impossible to control the glycosuria, even with 90 units of insulin daily. The concentration of sugar in the blood was 170 mg. The icteric index was 120. The value for amylase in the blood was 10.5 units. On March 2 the patient was given preoperative preparation with a continuous intravenous drip of a 5 per cent solution of dextrose, with 12 units of insulin for each 250 cc. of solution. He was operated on by Dr. Edwin Beer. A distended gallbladder and a hard nodule about half the size of a walnut in the head of the pancreas were found. There were no stones palpable in the common bile duct. A cholecystogastrostomy was performed. For the next three days a continuous intravenous drip of a 5 per cent solution of dextrose was administered. Eight units of insulin was administered for every 500 cc. of solution. During this period of continuous intravenous injection there were several attacks of disorientation accompanied by loud denunciation of those about him. On one occasion the temperature dropped to 97.4 F. On another occasion the sugar content was 25 mg. per hundred cubic centimeters of blood taken from one arm during continuous intravenous administration of dextrose. These symptoms disappeared on acceleration of the intravenous administration of dextrose. The administration of insulin was discontinued. During the next two days the urine contained 1.5 per cent sugar. The patient was then given a diet of 140 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat, with 45 units of insulin. On this regimen the urine was free from sugar. On March 7 the icteric index was 104; the total cholesterol content was 535 mg., and cholesterol esters, 310 mg., per hundred cubic centimeters of blood. By March 10 the icteric index had dropped to 68, the concentration of total cholesterol to 440 mg. and the esters to 235 mg. On March 17 the patient's urine was sugar-free, when the diet contained 140 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat with 10 units of insulin daily. The stool was well formed and soft; it contained urobilin. The icteric index was 45, the total cholesterol content, 440 mg. and esters, 290 mg. On March 21 the urine was sugar-free with a diet of 140 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat and no insulin. The concentration of blood sugar was 175 mg. per hundred cubic centimeters. The icteric index was 30, the total blood cholesterol, 470 mg., and esters, 340 mg. The amount of amylase in the blood, however, had risen to 31 units. On March 30 the urine was free from sugar with a diet of 200 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat and no insulin. The icteric index was 22, and the blood sugar content, 145 mg. The stools were dark and well formed. The patient's general condition was comparatively good. On April 2 he was given 1.5 Gm. of dextrose per kilogram of body weight with the following results:

Time	Blood Sugar, Mg. per 100 Cc.
After fasting.....	78
½ hour after dextrose.....	93
1 hour after dextrose.....	112
2 hours after dextrose.....	109
3 hours after dextrose.....	93

CASE 3.—A man aged 58 with no previous history of diabetes was admitted to the hospital for the first time on Jan. 14, 1934. For the past six weeks there

had been recurrent attacks of colicky pain in the right upper quadrant of the abdomen. Recently jaundice had appeared. There was an acute attack of pain, nausea and vomiting seven hours before admission to the hospital. On examination icterus was marked. The edge of the liver was palpable 2 inches (5 cm.) below the costal margin. Definite tenderness was elicited in the right upper quadrant. The urine contained 2.5 per cent sugar but no acetone. The blood pressure was 150 systolic and 70 diastolic, and there was evidence of cardiovascular disease. The stools were clay-colored. The content of blood sugar was 130 mg. and the total concentration of cholesterol, 275 mg., with cholesterol esters, 145 mg. per hundred cubic centimeters. The icteric index was 55, and the amylase in the blood, 12.5 units. The patient was given a diet of 250 Gm. of carbohydrate, 60 Gm. of protein and 40 Gm. of fat with 35 units of insulin. Control of the glycosuria was extremely difficult. There continued to be a 3 per cent excretion of sugar even when the dosage of insulin was raised to 90 units daily. As the clinical condition improved and the jaundice progressively diminished the sugar tolerance improved. The dosage of insulin was steadily reduced and then omitted. When the patient was discharged the icteric index was 12, and the urine was free from sugar with a diet of 300 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat and no insulin. The blood sugar after fasting was 120 mg.

The patient was seen three months later in the outpatient department. Two days before, he had been taken ill suddenly with acute abdominal pain in the right side radiating to the back and spreading diffusely over the abdomen. For two days the stools had been clay-colored and the patient had vomited once. There was slight icterus, and tenderness and rigidity were noted in the right upper quadrant. Tests of the urine gave positive results for bile and bilirubin. The urine contained 1 per cent sugar. A sugar tolerance curve was obtained the following day.

Time	Blood Sugar, Mg. per 100 Cc.
After fasting	95
½ hour after 100 Gm. of dextrose.....	190
1½ hours after 100 Gm. of dextrose.....	290
2½ hours after 100 Gm. of dextrose.....	230

The patient was admitted to the hospital the next day, May 5. The concentration of blood sugar was 130 mg. per hundred cubic centimeters. The total concentration of cholesterol was 250 mg. and the cholesterol esters, 50 mg. per hundred cubic centimeters of blood. The icteric index was 35. A direct van den Bergh test gave positive results, and an indirect van den Bergh test, 1:40,000. The stools were medium brown. The urine contained urobilin. The patient was under observation for two weeks. The glycosuria was controlled with a diet of 160 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat with 30 units of insulin daily. A laparotomy was performed on May 19. A large, abnormally brown, mottled liver was found. The gallbladder was distended and on aspiration foul, infected bile was obtained. No stones were palpable in the gallbladder or in the common bile duct. A cholecystostomy was performed. Postoperative biliary drainage was profuse, and the jaundice gradually disappeared, as did the urobilinuria. On May 24 the total cholesterol content was 250 mg. with traces of cholesterol ester. The icteric index was 27. By June 2 the icteric index had dropped to 18. On June 7 the total content of blood cholesterol was 235 mg. with an ester partition of 100 mg. The icteric index had dropped to 15, and the result of the indirect van den Bergh test to 1:300,000. During this time the tolerance for dextrose steadily improved. There was no postoperative glycosuria, and the

dosage of insulin was gradually reduced and finally omitted on June 1. On discharge the urine was sugar-free with a diet of 250 Gm. of carbohydrate, 60 Gm. of protein and 60 Gm. of fat with no insulin. The blood sugar was 100 mg. per hundred cubic centimeters. On the twenty-first day postoperatively the cholecystostomy tube was removed and about a dozen faceted stones were extruded through the sinus. The tube was reinserted, and the wound was irrigated daily. Five days later the tube was removed permanently. The drainage diminished appreciably and the patient was discharged forty-two days after the operation in excellent general condition. The test for sugar tolerance on June 21 with 1.75 Gm. of dextrose per kilogram of body weight (93 Gm.) gave the following results:

Time	Blood Sugar, Mg. per 100 Cc.
After fasting	100
50 minutes after dextrose.....	165
2 hours after dextrose.....	160
3 hours after dextrose.....	100

COMMENT

Examination of the foregoing protocols reveals certain interesting features. In all three cases there was no clinical manifestation of diabetes mellitus before the onset of disturbance in the biliary tract. The patient in case 1 had been under observation in the hospital eight months previously. There had been no evidence of diabetes. In case 2 the onset of the diabetic symptoms coincided with the appearance of jaundice. It is, of course, less significant that there was no previous history of diabetes in case 3. In each of the 3 instances the development of symptoms of disturbance in the biliary tract with associated impairment of function of the liver, as measured by the icteric index and the elevated blood cholesterol, had been accompanied by hyperglycemia and glycosuria. Adequate biliary drainage, regardless of the nature of the lesion, resulted in the return of the icteric index and cholesterol in the blood to relatively normal values. With the restoration of function of the liver tolerance for dextrose steadily improved. The dose of insulin could be progressively reduced and the administration of the drug then omitted. Subsequent tests for sugar tolerance following the ingestion of dextrose then revealed nondiabetic values. This striking correlation between the function of the liver and dextrose tolerance was particularly noteworthy in case 3; the patient was observed during two episodes. In case 2 the biliary obstruction was due to carcinoma of the head of the pancreas. The improvement in the diabetic status closely followed the fall in the icteric index and the blood cholesterol after cholecystogastrotomy. This improvement in tolerance for sugar occurred at the same time that the amount of amylase in the blood rose from 10.5 to 31 units. The rise in value for amylase is said to indicate progressive pancreatic damage. However, at the time of this maximum concentration of amylase in the blood the urine was sugar-free when the

patient was given a liberal diet with no insulin and the dextrose tolerance curve was normal. If the glycosuria in biliary disease is to be explained on the basis of pancreatic damage no such inverse relationship would be anticipated.

Another interesting feature was the comparative resistance to insulin in cases 2 and 3 during the periods of marked impairment of the liver. The development of hypoglycemia postoperatively in cases 1 and 2 with relatively small doses of insulin seems paradoxical at first. These two findings can be reconciled most satisfactorily by a consideration of the blood sugar-regulating mechanism of the liver.

The level of sugar in the blood is maintained by a balanced equilibrium between the dextrose entering and the dextrose leaving the blood stream. The chief stores of the dextrose entering the blood stream are, first, the alimentary canal through the portal venous system and, second, the glycogen stores in the body, chief of which is the liver. Dextrose leaving the blood stream may go to the liver as the glycogen reserve; it may be burned directly in the resting metabolism of the tissues; it may go to the muscle and enter into reactions there or it may be converted to fat and stored as such. It is significant to observe that of the four chief processes into which dextrose enters after leaving the blood stream, only the first is reversible, the liver glycogen thereby being made available for the maintenance of the level of blood sugar.

When this equilibrium is disturbed at any one of its various points the end-result is either hyperglycemia or hypoglycemia, depending on the direction of the disturbance of the equilibrium. The liver is the chief organ concerned directly with the removal of dextrose from the blood stream as well as with its return to the blood stream when necessary. This regulation is under the control of antagonistic hormones, of which insulin and epinephrine are the most important, but in spite of the normal presence of hormones the liver itself must be functioning adequately to respond to the stimuli of these hormones. It will be noted that in case 1 insulin shock was accompanied by a sharp rise in blood pressure. This was probably due to the compensatory discharge of epinephrine in an effort to restore the normal level of blood sugar. The amount of epinephrine necessary to elevate the systolic blood pressure 90 mm. must have been enormous, but it apparently had no effect in overcoming the hypoglycemia. Loeb, Reeve and Glasier¹⁵ pointed out that the rise in the content of blood sugar following the injection of epinephrine is less marked in persons with disease of the liver and diabetes than in normal persons, a finding, which is again

15. Loeb, R. F.; Reeve, E. B., and Glasier, H. P.: *J. Clin. Investigation* 10:19, 1931.

consistent with the knowledge of the liver as a blood sugar-regulating mechanism. In totally hepatectomized animals epinephrine is not effective in overcoming the hypoglycemia.

The laparotomy in case 3 revealed a marked degree of hepatitis, which was consistent with the low values for cholesterol esters in the blood.¹⁶ Similar observations in the case of Himsworth and in that of Baker and Rynearson have been cited. It is a common observation of pathologists that prolonged disease of the biliary tract results in extensive hepatitis, but it is, of course, equally true that biliary stasis may also be associated with pancreatitis.

In each of these cases when the patient was first seen the hyperglycemia and glycosuria necessitated a tentative diagnosis of diabetes. In case 2 this was confirmed by a test for dextrose tolerance. Following drainage of the biliary tract and the restoration of function of the liver, glycosuria and hyperglycemia disappeared in spite of a liberal diet, and the values for dextrose tolerance became normal. The normal reaction to the dextrose tolerance test is particularly significant in the interpretation of the disturbance of carbohydrate metabolism. Joslin has recognized its value in the differentiation of true diabetes but has warned of the danger of basing any clinical diagnosis on a single laboratory procedure. Peters and Van Slyke¹⁷ stated that a normal response to the test may be accepted as fairly conclusive evidence against any degree of diabetes. Powelson and Wilder¹⁸ found the simple test for dextrose tolerance to be a reliable means of differentiating benign glycosuria from true diabetes. Of 82 cases in which the diagnosis of normoglycemic glycosuria was made on the basis of this test, diabetes did not develop in any in the intervals of from one to twelve years that elapsed after the tests were made.

Although the normal reaction to the test for dextrose tolerance may be accepted as fair evidence for the exclusion of true diabetes, it does not rule out the possibility of other preceding transitory disturbances which might affect carbohydrate metabolism. However, neither temporary derangement of islet function nor infection can explain the favorable influence of biliary drainage in case 2. The carcinoma of the head of the pancreas remained intact, and the values for amylase in the blood indicated progressive pancreatic damage, although there was a complete restoration of dextrose tolerance. The striking direct correlation between sugar tolerance and liver function in each of the 3

16. Epstein, E. Z.: Cholesterol of the Blood Plasma in Hepatic and Biliary Disease, *Arch. Int. Med.* **50**:203 (Aug.) 1932.

17. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1931, vol. 1.

18. Powelson, H. C., and Wilder, R. M.: Innocent Glycosuria, *J. A. M. A.* **96**:1562 (May 9) 1931.

cases reported here suggests the possibility that the glycosuria and hyperglycemia may not necessarily be manifestations of hypo-insulinism.

That the clinical picture of diabetes can exist with normal production of insulin and its attendant ability to oxidize dextrose is not a novel conception. Du Bois¹⁹ and Sanger and Hun²⁰ have noted hyperglycemia and glycosuria in patients with hyperthyroidism who presented the clinical features of diabetes. Studies of the respiratory quotient, however, indicated that there was no impairment of the ability to oxidize carbohydrates. In an analogous manner it might be said that the clinical manifestations of diabetes encountered in these 3 cases of disease of the biliary tract may be interpreted on the basis of the associated disturbances of the function of the liver and that it may not be necessary to postulate the existence of hypo-insulinism. The recent development of the laboratory evidence of the function of the liver in the maintenance of the level of blood sugar offers a logical explanation of our observations.

The classic work of Mann, Magath and their associates²¹ has demonstrated that the maintenance of the blood sugar is dependent on the presence of an adequately functioning liver. When the liver is removed from an animal there is a progressive decrease in the concentration of sugar in the blood to the point of hypoglycemia and death. This fact holds true in animals with an intact pancreas as well as in those which have been rendered diabetic by the previous removal of the pancreas. These experiments illustrate one phase of the function of the liver in the maintenance of the level of blood sugar, i. e., as the source which slowly but constantly releases the dextrose to maintain the normal concentration.

Pollack, Millet, Bollman and Wilder²² demonstrated another function of the liver which has been confirmed by Soskin and his co-workers.²³ They subjected totally hepatectomized animals to the constant intravenous injection of dextrose. When the dextrose was injected at the rate of from 0.1 to 0.25 Gm. for each kilogram of body weight during each hour, a rate at which the animal can consume immediately practically all the dextrose so given, the values for blood sugar remained in the normal range. When, however, the rate of injection was such

19. Du Bois, E.: Clinical Calorimetry, *Arch. Int. Med.* **17**:915 (June) 1916.

20. Sanger, B. J., and Hun, E.: Glucose Mobilization Rate in Hyperthyroidism, *Arch. Int. Med.* **30**:397 (Oct.) 1922.

21. Mann, F. C., and Magath, T. B.: Effect of Removal of the Liver on the Blood Sugar Level, *Arch. Int. Med.* **30**:73 (July) 1922; *ibid.* **31**:797 (June) 1923. Mann, F. C.: Effect of Total Removal of the Liver After Pancreatectomy on the Blood Sugar Level, *Medicine* **6**:419, 1927.

22. Pollack, H.; Millet, R.; Bollman, J. L., and Wilder, R. M., Jr.: *Proc. Staff Meet., Mayo Clin.* **8**:557, 1933.

23. Soskin, S.; Allweiss, M. D., and Cohn, D. J.: *Am. J. Physiol.* **109**:55, 1934. Soskin, S., and Allweiss, M. D.: *ibid.* **110**:4, 1934.

as to introduce 2 Gm. of dextrose for each kilogram of body weight during each hour, a rate which far exceeds the maximum rate of immediate utilization, then the values for blood sugar were in the range of those found in diabetic animals. Thus, the picture of diabetes, as far as the concentration of sugar in the blood and urine is a criterion, was reproduced by removal of the liver and giving dextrose at a rate beyond the maximum rates of immediate utilization. From previous studies on the respiratory quotient by Mann and Boothby²⁴ it was evident that there was no interference with the ability of these animals to oxidize dextrose. Hence, it can be said that these hepatectomized animals were not truly diabetic, even though their tolerance for dextrose indicated that this might be the case.

These remarks are in no way intended to depreciate the value of insulin in the maintenance of the normal carbohydrate cycle. The aforementioned experiments are based on the required presence of insulin. They do emphasize, however, that in spite of adequate amounts of insulin, unless the liver is capable of removing the dextrose from the blood stream the values for blood sugar will mount and hyperglycemia comparable to that found in cases of diabetes will occur.

The clinical significance of the liver in cases of disturbance of carbohydrate metabolism has long been recognized. In Claude Bernard's classic monograph "*Leçons sur le diabétique*"²⁵ he noted a most interesting case. His patient had had well developed diabetes mellitus for years. With the gradual onset of cirrhosis of the liver the clinical picture of diabetes disappeared. Bordley²⁶ at the Johns Hopkins Hospital recently noted a case of a similar condition. Extensive destruction of the liver by carcinoma, both primary and metastatic, has been reported from three different groups as being associated with marked hypoglycemia. Clinically these cases resembled those of hyperinsulinism, and yet on postmortem examination pancreatic disease was not found but there was destruction of the major part of the liver. Judd, Kepler and Rynearson²⁷ have reported 2 cases of spontaneous hypoglycemia. Biopsy on material from the liver in these 2 cases revealed obvious gross and microscopic damage. Hypoglycemia has been observed in patients with acute hepatitis caused by arsphenamine, acute yellow atrophy of the liver and thrombosis of the hepatic artery.

Disease of the liver not only may produce hypoglycemia but may cause resistance to insulin in persons known to have diabetes. This was

24. Mann, F. C., and Boothby, W. M.: *Am. J. Physiol.* **87**:486 (Dec.) 1928.

25. Bernard, C.: *Leçons sur le diabète et la glycogénèse animale*, Paris, J. B. Baillière et fils, 1877, p. 355.

26. Bordley, J. H.: *Bull. Johns Hopkins Hosp.* **47**:113 (Aug.) 1930.

27. Judd, E. S.; Kepler, E. J., and Rynearson, E. H.: *Am. J. Surg.* **24**:345, 1934.

true in the cases reported by Pollack and Long²⁸ as well as in the one reported by Judd, Kepler and Rynearson. Resistance to insulin in cases of hemochromatosis after the development of cirrhosis of the liver is well known. Root,²⁹ Pollack³⁰ and MacBryde³¹ have called attention to the rôle of the liver in the development of resistance to insulin. In Himsworth's case¹² of severe refractory diabetes autopsy revealed a grossly damaged liver and a normal pancreas.

SUMMARY

The experimental studies on the liver as a blood sugar-regulating mechanism are of significance in the interpretation of the hyperglycemia and glycosuria of disease of the biliary tract. In each of our 3 cases there was a direct correlation between the disturbance of carbohydrate metabolism and the degree of impairment of hepatic function. The restoration of normal function of the liver by adequate biliary drainage not only resulted in the disappearance of the diabetic manifestations, but the ingestion of dextrose was followed by normal values for sugar tolerance. The normal response to a test for sugar tolerance may be accepted as excluding true diabetes mellitus. The possibility of transient impairment of tissue of the pancreatic island will not explain the restoration of normal tolerance for sugar following biliary drainage in the case of carcinoma of the head of the pancreas. It is, therefore, suggested that the disturbance of carbohydrate metabolism in these 3 cases may be explained on the basis of a disturbance of the function of the liver as a blood sugar-regulating mechanism. Studies on the respiratory quotient should be carried out to determine whether there is actual impairment of the ability of these patients to oxidize dextrose.

One cannot deny the coexistence of disease of the gallbladder and true diabetes mellitus. The restoration of the normal value for dextrose tolerance is a criterion for differential diagnosis. It is, perhaps, significant that each of our patients was seen during his first attack of disease of the biliary tract. It is possible that repeated or prolonged attacks of disease of the biliary tract might produce permanent damage to the mechanisms regulating the blood sugar. It seems reasonable, especially in the light of recent experimental evidence, to assume that a disturbance of carbohydrate metabolism with complete restoration following biliary drainage as in these 3 cases may be interpreted on the basis of hepatic dysfunction.

28. Pollack, H., and Long, E. P.: Thrombosis of the Hepatic Artery with Sudden Resistance to Insulin in a Diabetic Patient, *Arch. Path.* **13**:530 (March) 1932.

29. Root, H.: *New England J. Med.* **201**:201, 1929.

30. Pollack, H.: *Proc. Staff Meet., Mayo Clin.* **8**:453, 1933.

31. MacBryde, C. M.: Insulin Resistance in Diabetes Mellitus, *Arch. Int. Med.* **52**:932 (Dec.) 1933.

IDIOPATHIC STEATORRHEA

METABOLIC STUDY OF A PATIENT, WITH REFERENCE TO THE UTILIZATION OF NITROGEN AND FAT

JAMES F. WEIR, M.D.

AND

MILDRED ADAMS, PH.D.

ROCHESTER, MINN.

Steatorrhea is a prominent feature of a number of relatively uncommon diseases, among which may be mentioned sprue (tropical and nontropical) and celiac disease (Gee and Herter). In his recent monograph on idiopathic steatorrhea, Thaysen¹ attempted to prove that tropical sprue, nontropical sprue and celiac disease are manifestations of the same pathologic process. Others also have challenged the idea that sprue is a purely tropical disease and of restricted distribution. That the nontropical form of the disease is being more frequently recognized and reported is indicated by the articles of Thaysen,¹ Bennett, Hunter and Vaughan² and Mackie.³ The last-mentioned author was able to collect reports of seventy-one cases from the literature. Other cases are known, and the condition is probably more common than is generally believed.

This syndrome must be distinguished from other types of diarrhea, among which is the type that is the result of pancreatic deficiency (external secretion). In the latter condition azatorrhea is also present, there is a greater loss of fat in the stools than there is in the idiopathic form, and the percentage of fatty acids is higher. In idiopathic steatorrhea the widespread nature of the systemic involvement (gastro-intestinal, hematologic, neurologic and metabolic) produces a variety of symptoms that are difficult to explain from a pathogenic standpoint. Similarly, there has been confusion regarding therapeutic procedures, especially the innumerable types of diet and the effects of vitamins, calcium, liver, iron, arsenic and hydrochloric acid. The results have

From the Division of Medicine and the Section on Clinical Metabolism, the Mayo Clinic.

1. Thaysen, T. E. Hess: *Non-Tropical Sprue: A Study in Idiopathic Steatorrhoea*, New York, Oxford University Press, 1932.

2. Bennett, T. I.; Hunter, Donald, and Vaughan, J. M.: *Idiopathic Steatorrhea (Gee's Disease): A Nutritional Disturbance Associated with Tetany, Osteomalacia and Anaemia*, *Quart. J. Med.* **1**:603 (Oct.) 1932.

3. Mackie, Thomas T.: *Nontropical Sprue*, *M. Clin. North America* **17**:165 (July) 1933.

been variable. This all suggests that the pathogenesis of the disease is very uncertain. There are many symptoms that suggest a relationship to pernicious anemia. The work which has been done on sprue by Castle and Rhoads⁴ and their associates indicates that the disease involves a deficiency of an intrinsic gastric factor. This result would seem to aid in discovering the disease process and in working out a therapy. Rhoads and Miller⁵ pointed out that clinical sprue may arise in three ways: (1) by dietary lack; (2) by lack of the gastric enzyme that is absent in pernicious anemia, or (3) by inability to absorb the product of the interaction of the dietary and gastric factors. They admitted the emphasis which has been placed on the hematologic side, but they pointed out the simultaneous improvement in the lingual and gastro-intestinal symptoms, which was similar to that which had been observed by Minot and Murphy in pernicious anemia. They expressed the opinion that any dietary regimen that offers improvement does so by supplying an increased amount of the water-soluble vitamin, but in a very uncertain manner. These workers and others have demonstrated that the typical response of the reticulocytes occurs in sprue, as well as in pernicious anemia, when adequate amounts of the intrinsic factor are supplied.

Whether or not these observations are accepted, the fact remains that in steatorrhea an excess of fat occurs in the stools. In the literature, there is a controversy as to whether this condition is attributable to defective absorption, in spite of efficient hydrolysis, or to massive reexcretion of fat into the colon after the absorption in the small intestine has been relatively normal. In patients who were observed personally by Thaysen,¹ the output of fat for twenty-four hours varied from 15.9 Gm. to 66.7 Gm. The average was 36.59 Gm., which was about triple the average daily output for normal persons. The average loss, furthermore, was about a third of the fat which was ingested. He discovered that in individual cases the output of fat increased with increased intake of fats. Fatty acids made up the largest component of the output of fat; neutral fat came next, and the soaps were the smallest component. This, however, varied greatly in different cases and at different times. In most cases the output of nitrogen in the feces, for twenty-four hours, was below 3 Gm. These figures are in agreement with the analyses that have been published by other workers.

When the patient whose case is described in this report presented himself, an excellent opportunity was offered for a detailed study of the metabolism of fat and nitrogen, because the condition was well developed

4. Castle, W. B., and Rhoads, C. P.: The Aetiology and Treatment of Sprue in Porto Rico, *Lancet* **1**:1198 (June 4) 1932.

5. Rhoads, C. P., and Miller, D. K.: Intensive Liver Extract Therapy of Sprue, *J. A. M. A.* **103**:387 (Aug. 11) 1934.

and there were marked hematologic and neurologic symptoms. The patient was intelligent and cooperative.

Because of the loss of weight, the edema and the diarrhea, we hoped to be able to determine the time that was required to restore nitrogen balance, the extent of absorption of nitrogen, the extent of positive balance attained on a diet rich in protein and the effect of the diet on the serum protein content, the edema and the weight. The condition suggested a study of the output of fat when the intake was known and of the effect which was produced on the output by increasing the intake of the amount of fat which was excreted when diarrhea was controlled clinically and, finally, of any demonstrable effect on the rate of absorption after administration of liver extract, which obviously was indicated by the degree and type of anemia and by the neurologic changes.

REPORT OF A CASE

History.—A white man, aged 26, was seen first in March 1934. He had developed normally until the age of 15; since then there had been little growth. For the past ten years he had suffered recurring attacks of anorexia, diarrhea, bloating, abdominal discomfort, fatigue, loss of weight and pallor. The first two or three stools in the morning were bulky and gray; subsequent stools were watery. During the attacks from four to five stools were passed daily, and this persisted for a month or more. Between attacks, constipation frequently was present. In spite of the attacks, he continued through high school and entered a university, but after the first year he was forced to leave for two years. At that time he had his tonsils and appendix removed (at the age of 18). After some improvement he returned to the university and graduated in 1932, at the head of his class. However, since then he had been worse and was unable to work. The attack which caused him to come to the clinic had begun five months previously and was associated with numbness and tingling in the hands and feet and clumsiness and incoordination of the fingers, which had persisted for two months.

Two years before this attack he had a sore tongue and mouth for one month. Anemia was present at various times. His weight varied; the most he had weighed was 115 pounds (52 Kg.), but the usual weight was 110 pounds (50 Kg.). Various therapeutic agents had been tried; these included nourishing diets, fruit juices, dairy products, vitamins, iron, liver and hydrochloric acid.

Physical Examination.—The patient was 5 feet and 3 inches (160.02 cm.) in height and weighed 90 pounds (40.8 Kg.). He was definitely dwarfed and undernourished. Weakness, moderate pallor, moderate edema, clubbed fingers and a doughy, distended abdomen were prominent features. The gums disclosed reddened areas and bled easily. The pupils were irregular and unequal and did not react to light. Neurologic examination gave evidence of subacute combined sclerosis, which was well defined. Proctoscopic examination revealed mild proctitis. Roentgenologic examination of the gastro-intestinal tract disclosed a normal stomach and duodenum, slight dilatation and hypomotility of the small intestine and a spastic and slightly dilated colon. In the colon the haustral churning was absent distal to the hepatic flexure.

The urine was normal. The concentration of hemoglobin was 10.3 Gm. per hundred cubic centimeters (62 per cent); the erythrocytes numbered 2,580,000, and the leukocytes, 2,700, per cubic millimeter of blood. The differential count

was as follows: lymphocytes, 30 per cent; mononuclears, 6.5 per cent, and polymorphonuclear neutrophils, 63.5 per cent. There were 4.4 per cent reticulocytes. Macrocytosis, very slight poikilocytosis, moderate anisocytosis, slight polychromatophilia, Howell-Jolly bodies and basophilic stippling were present. In general, the blood smear presented the picture of pernicious anemia, but it lacked evidence of any shift of the neutrophils to the right. The stools were bulky, gray and pasty in appearance, but examination of fresh specimens did not show parasites. Serologic examination did not reveal syphilis. Analysis of the gastric contents disclosed total acidity of 38 cc. and free hydrochloric acid of 22 cc. of tenth-normal solution of sodium hydroxide. Roentgenograms of the skull, forearms, wrists and pelvis demonstrated slight osteoporosis. The value for urea was 28 mg. and that for sugar was 70 mg. per hundred cubic centimeters of whole blood. Quantitative determinations with the blood serum gave the following values: for calcium, 7.8 mg. per hundred cubic centimeters; for phosphorus, 3.4 mg., and for protein, 4.9 Gm. The value for cholesterol was 93 mg. per hundred cubic centimeters of plasma; that for lipoids, 379.4 mg., and that for fatty acids, 286.4 mg. The albumin-globulin ratio was 1.2:1. The concentration of bilirubin was 1.3 mg. per hundred cubic centimeters of serum, as shown by the indirect van den Bergh test. The bromsulphalein test of liver function gave normal results. The basal metabolic rate was — 3.

Course.—As a result of treatment, which consisted of the administration of a diet low in fat and high in proteins, calcium, viosterol and liver extract and which was carried out during the investigative procedures, there took place diuresis, disappearance of edema, a temporary decrease in weight that was followed by an increase, gain in strength, marked improvement in the gastro-intestinal condition, disappearance of evidence of inflammatory changes in the oral and the intestinal mucous membranes, typical reticulocytosis, improvement of the anemia and marked improvement in the neurologic symptoms and signs.

When the man was seen three months later, his weight was 104 pounds (47.2 Kg.), and his color was good. His bowels had been moving twice daily, morning and evening, and the stools were normal in color and consistency and were not bulky. There had not been any recurrence of edema or sore tongue. Paresthesia had practically disappeared, but the patient still tired easily. The concentration of hemoglobin was 12.9 Gm. (77 per cent); the erythrocytes numbered 4,320,000, and the leukocytes, 5,100, per cubic millimeter of blood. The blood smears revealed hypochromic anemia but did not disclose the features of pernicious anemia, which previously were present. The sensory disturbances were much improved, but no definite improvement was noted in the reflexes on neurologic examination.

Results.—During the first three periods of four days the average daily intake of protein was 82 Gm. With this intake the patient maintained a positive nitrogen balance from the start. The amount of retained nitrogen was high and was fairly uniform. With the increase of the intake of protein to 101 Gm. in the fourth period, the nitrogen balance increased to +3.73 Gm. This was a slight increase over the average of the preceding twelve days (+3.27 Gm.), but it was not as high as that which was obtained in the second period (+3.92 Gm.). In the fifth period the fat was materially increased for one day; however, the patient was unable to eat this food, and it had to be varied from day to day. The intake for this period, therefore, is not as accurately known as that for the other periods. With the clinical upset, there was a definite decrease in retention of nitrogen, although the intake of nitrogen was no less than it was in the first period. In the sixth period, the general condition of the patient was much better; he ate all

of the food, including the increased amount of fat and protein, and he had a very definite retention of nitrogen, which averaged 4.64 Gm. daily. It is difficult to state whether this was the result of the increased intake of nitrogen or of the change in the clinical condition of the patient. The daily amount of nitrogen in the feces was considerably higher than that which has been observed frequently as normal on a diet of a similar protein content. In spite of this rather high content of nitrogen in the feces, the patient was able to utilize sufficient protein to store considerable amounts.

During this period of moderately high intake of protein there were mild diuresis, disappearance of edema and some loss of weight. On continuation of the treatment after completion of the experiment, the weight gradually increased. The serum protein increased from 4.9 Gm. at the beginning of the experiment to 5.4 Gm. at the completion.

From a metabolic as well as from a gastro-intestinal standpoint, it is evident that the patient satisfactorily tolerated the high intake of protein and that this, combined with the other procedures, produced beneficial results.

With the low intake of fat (44 Gm. daily), the number of daily stools was reduced from three to one after the first two periods. Throughout the six periods excessive amounts of fat were present in the feces. Fowweather,⁶ as the result of an investigation of the normal fat content of the stools of eighty-four adults, suggested that any specimen in which the total fat exceeds 28 per cent of the total dry matter is probably abnormal. In our case the fecal fat content definitely exceeded this value in all six periods, and the minimal excretion of fat was 33 per cent. With each increase in the daily intake of fat there were a decrease in the utilization and an increase in the output of fat. The amount of fat that was utilized, which was calculated from the difference between the intake and the output, varied relatively little with the intake except during the fifth period. Coincident with the marked gastro-intestinal upset which occurred in this period, there was a marked decrease in the utilization of fat. The small variations which occurred in the other periods suggest that, under these conditions at least, about 25 Gm. of fat is the maximal amount which can be utilized. With the increase in the output of fat the stools tended to become more frequent and became looser and bulkier. It was discovered that the patient could not tolerate 70 Gm. of fat daily but that 50 Gm. caused no marked disturbance.

Administration of liver extract produced reticulocytosis. This began early in the second period of observation and terminated in the fifth period. Whether the liver extract or the low intake of fat played the greater part in reducing the frequency of the stools in the third and fourth periods may be open to question, but we believe that it was the latter factor, because an increase in the intake of fat produced an increase in both the number and the size of the stools in spite of the continued effects of liver extract and its continued administration. If the intake of fat had been increased gradually before administration of liver extract, it is possible though improbable that there may have been a greater loss of fat in the stools. Furthermore, the positive nitrogen balance disclosed no changes which were parallel to the reticulocytosis.

Summary of Chemical Investigation.—The patient was placed in the hospital. The urine and feces were accurately collected in four day

6. Fowweather, F. S.: The Determination of the Amount and the Composition of the Fat of Faeces: I. Investigation of a "Wet" Method and Comparison with the "Dry" Method, *Brit. J. Exper. Path.* 7:15 (Feb.) 1926.

periods and analyzed, as is shown in tables 1 and 2, to determine the daily output of nitrogen and the total lipoids. Diets were accurately weighed, and the intake of protein, of fat and of calories was determined by analysis.

The amount of nitrogen in the food, in the fat and in the feces was determined by the Kjeldahl method. The total fat was determined by the method of Kumagawa and Suto.⁷ This is based on a preliminary saponification and followed by acidification, extraction with ethyl ether and finally reextraction with petroleum ether. It therefore includes the

TABLE 1.—*Showing Number of Stools, Weight of Patient and Reticulocyte Count*

Period	Date	Stools	Weight of Patient		Reticulocytes (per Cent)
			(Lb.)	(Kg.)	
I	March 12...	3	93.0	42.2	2.3
	March 13...	3	92.0	41.7	1.4
	March 14...	3	91.5	41.5	1.5
	March 15...	3	91.0	41.3	2.8
II	March 16...	3	91.5	41.5	8.4
	March 17...	2	92.5	41.9	10.2
	March 18...	2	92.5	41.9	11.8
	March 19...	2	91.0	41.3	10.6
III	March 20...	1	91.5	41.5
	March 21...	1	90.0	40.8	11.5
	March 22...	1	89.25	40.5	11.2
	March 23...	1	89.0	40.4	12.5
IV	March 24...	1	89.25	40.5	6.5
	March 25...	1	89.5	40.6	4.2
	March 26...	1	90.25	40.9	3.5
	March 27...	1	90.5	40.9	3.0
V	March 28...	1	91.0	41.0	2.7
	March 29...	1	89.5	40.6	3.2
	March 30...	2	91.0	41.3	1.8
	March 31...	1	91.0	41.3	1.5
	April 1....	2	90.75	41.1
VI	April 2....	2	92.0	41.7	2.3
	April 3...	1	93.0	42.2	1.9
	April 4...	2	92.5	41.9	2.6
	April 5...	1	93.0	42.2	2.7

nonsaponifiable portion as well as the neutral fat, the soap and the free fatty acids. Daily determinations of creatinine were made to insure complete collections of the twenty-four hour specimens of urine.

The time of observation was divided into six periods of four days each. The first two periods were controls; in these, the average daily intake was 80 Gm. of protein, 44 Gm. of fat and sufficient carbohydrate to give a total of approximately 1,800 calories. In the third period, viosterol, 15 drops three times a day, and calcium lactate, 1 drachm (4 Gm.) three times a day, were added. Administration of these

7. Kumagawa, Muneo, and Suto, Kenzo: Ein neues Verfahren zur quantitativen Bestimmung des Fettes und der unverseifbaren Substanzen in tierischen Material nebst der Kritik einiger gebräuchlichen Methoden, *Biochem. Ztschr.* 8:212, 1908.

continued throughout the experiment. In the fourth period the diet was increased to 101 Gm. of protein, 50 Gm. of fat and sufficient carbohydrate to supply a total of 2,080 calories. In the fifth period the diet was again increased, but there was a gastro-intestinal upset which prevented the patient from taking all his food and required reduction in the amount consumed. However, he recovered quickly, and in the sixth period he readily tolerated a diet of 122 Gm. of protein, 70 Gm. of fat and sufficient carbohydrate to furnish 2,646 calories.

TABLE 2.—*Showing Results of Chemical Examination of Stools and Other Data*

	Period I, March 12 to 15	Period II, March 16 to 19	Period III, March 20 to 23	Period IV, March 24 to 27	Period V, March 28 to April 1	Period VI, April 2 to 5
Intake of nitrogen, Gm. daily.....	12.34	13.22	13.22	16.14	12.56	19.49
Nitrogen in urine, Gm. daily.....	6.95	6.41	8.02	9.31	8.94	11.59
Nitrogen in feces, Gm. daily.....	2.08	2.89	2.61	3.10	2.89	3.26
Output of nitrogen, Gm. daily.....	9.03	9.30	10.63	12.41	11.83	14.85
Nitrogen balance	+3.31	+3.92	+2.59	+3.73	+0.73	+4.64
Total intake of fat, Gm. daily.....	38.90	40.20	40.20	47.30	35.60	66.60
Total output of fat, Gm. daily.....	13.50	15.10	19.40	23.90	21.30	39.00
Fat in feces, per cent of dry weight	36.60	32.70	39.00	40.60	39.10	50.00
Total fat utilized, Gm. daily.....	25.40	25.10	20.80	23.40	14.30	27.60
Weight of patient (beginning {Kg.. of period) }Lb..	42.20 93.00	41.50 91.50	41.50 91.50	40.50 89.25	41.30 91.00	41.70 92.00
Preformed creatinine in urine, Gm. daily	0.319	0.295	0.308	0.313	0.234	0.320
Total calories in daily intake of food	1,812	1,812	1,812	2,080	2,646
Diet*	1	1	1	2	3	3
Liver extract, daily.....	2 to 3 cc.			3 cc.		
			15 minims viosterol and 2 drachms (8 cc.) cal- cium lactate daily	Same medi- cation	Not all food eaten the first day; diet 1 given the second, third and fourth days; diet 2 given on the fifth day	.

* Diet 1 contained: protein, 80 Gm.; fat, 44 Gm., and sufficient carbohydrate to furnish a total of approximately 1,800 calories. Diet 2 contained: protein, 101 Gm.; fat, 50 Gm., and sufficient carbohydrate to furnish approximately 2,080 calories. Diet 3 contained: protein, 122 Gm.; fat, 70 Gm., and sufficient carbohydrate to furnish approximately 2,646 calories.

During the first period the patient received daily intramuscular injections of liver extract, which amounted to 13.5 cc. Nine cubic centimeters, in divided doses, was given during the fourth period. Daily estimation of the reticulocytes and frequent blood counts were made. Daily records of the weight, the volume of urine and the number of stools also were made.

COMMENT

In our clinical experience with cases of this type it has been apparent that little can be accomplished unless control of the diarrhea can be attained. Diet is an important factor in this consideration. Thaysen¹ has said that there is hardly any form of diet, from the most liberal

to the most restricted, that has not been recommended. Although the diets differ greatly, all have given good results according to various investigators. It also must be remembered that patients with this condition have a tendency to recover spontaneously from the attacks. Therefore, it is possible that the importance of diet has been overestimated. However, our observations in this experiment tend to confirm the principle that any diet should contain at least a low amount of fat. An excess of fat tends to pass through the intestine and carries with it calcium, phosphorus, vitamins and possibly some products of digestion of protein, in addition to causing the patient subjective discomfort and annoyance. A high intake of protein seems advisable for the following reasons: 1. The level of serum proteins must be maintained to prevent or relieve any nutritional edema. 2. An excess of nitrogen must be supplied to the tissues to overcome their depleted condition; the high nitrogen balance in this case suggests that there had been a previous loss of tissue proteins. 3. If the work of Castle⁴ and his associates is accepted, the element of dietary lack may be overcome by an excess of the extrinsic factor which is of protein origin, and a high intake of protein of itself may be sufficient to maintain normal hematopoiesis in the milder cases.

SUMMARY

Data on a metabolic study of a case of nontropical sprue, which was featured by steatorrhea, diarrhea and hematologic, neurologic and nutritional changes, are presented. The loss of fat in the stools corresponds to that which has been reported by other investigators. A low tolerance for fat was present. When the intake of fat was increased, the amount of fat in the feces was increased. A low intake of fat reduced the frequency of stools to normal and relieved many of the gastrointestinal symptoms. With a moderately high intake of protein, the patient was able to store nitrogen in spite of rather high loss of nitrogen in the feces. An increase of the serum protein occurred with resulting diuresis, loss of edema and temporary loss of weight. Positive evidence of change in the absorption of fat or of protein did not result from the administration of liver extract in this case. The patient made marked clinical improvement as a result of the therapy used.

TULAREMIA

REPORT OF THREE FATAL CASES WITH AUTOPSIES

ALAN BERNSTEIN, M.D.

Assistant Resident in Medicine, Johns Hopkins Hospital

BALTIMORE

Within a period of two years, three fatal cases of tularemia have been observed at the Johns Hopkins Hospital. It is my purpose in this communication to report the clinical and pathologic data furnished by these three cases. The account graphically illustrates the evolution of the recognition of a disease the identity of which has only recently been established.

The first patient died without a definite clinical diagnosis. Miliary tuberculosis seemed the most likely of the many diseases suggested, among which tularemia was not included. The pathologic changes were at first not definitely identified. The second case, occurring a year later, was diagnosed clinically only shortly before death, when a hitherto neglected primary lesion attracted attention. A more careful inquiry then elicited the story that shortly before the onset of his illness the patient had injured his thumb while skinning a wild rabbit. So strikingly did the results of the autopsy resemble those in the previous case that the identity of the disease in both was now apparent. Finally, after an interval of another year, a third patient was admitted to the hospital with a clinical picture so similar to that presented by the other two that tularemia was immediately suspected; and the suspicion was soon verified.

Up to the present time, autopsies on eighteen patients who died of tularemia have been recorded. From these the following important data are summarized (table):

Verbrycke¹ reported the case of a woman whose illness began with jaundice and who was operated on for disease of the gallbladder before the true nature of her ailment was recognized. The second and third cases were reported by Francis and Callender.² In one case the disease had a chronic course, and death occurred almost five months after the onset of the illness. Bardon and Berdez³ contributed the account of the

From the Medical Clinic, Johns Hopkins University and Hospital.

1. Verbrycke, J. R.: Tularemia, with Report of a Fatal Case Simulating Cholangitis, with Postmortem Report, *J. A. M. A.* **82**:1577 (May 17) 1924.

2. Francis, E., and Callender, G. R.: Tularemia; Microscopic Changes of the Lesions in Man, *Arch. Path.* **3**:577 (April) 1927.

3. Bardon, R., and Berdez, G.: Tularemia: Report of a Fatal Case with Postmortem Observations, *J. A. M. A.* **90**:1369 (April 28) 1928.

Summary of Reported Cases of Fatal Tularemia with Autopsies

Case	Authors	Sex	Color	Age	Contact	Duration of Illness, Days	Clinical Characteristics	Pathologic Changes	Comment
1	Verbyrke.....	F	W	67	Rabbit	18	Jaundice	Lungs, spleen and lymph glands studded with nodules	
2	Francis and Callender.....	F	N	35	Rabbit	5 mo.	Chronic course	Lesions in lungs, liver, spleen and lymph nodes, some of which contained giant cells	
3	Francis and Callender.....	M	W	52	Fly bite	26	Terminal pneumonia	Spleen filled with nodules; surface of liver normal	Incomplete autopsy; only gross examination of liver and spleen
4	Burdon and Berdez.....	M	W	53	Rabbit	16	Bronchopneumonia	Lesions in lungs, spleen and liver	
5	Goodpasture and House.....	M	W	29	Rabbit	13	Generalized infection	Lesions in liver, spleen and lymph nodes	
6	Pahner and Hunsmann.....	F	W	?	Rabbit	9	Rapid course	Lesions in liver, spleen and lymph nodes; lungs congested, but no foci of necrosis	
7	Stimpson.....	M	N	25	Rabbit	4	Fulminant course	Lesions in lymph glands, spleen, liver and lungs	
8	Bunker and Smith.....	M	W	65	Rabbit	14	Bronchopneumonia	Lesions in lymph nodes, lungs and spleen	
9	Massee.....	M	W	40	Rabbit	18	Bronchopneumonia	Lesions in liver and spleen; confluent bronchopneumonia	
10	Hunkelp and O'Neil.....	M	W	45	Rabbit and squirrel	18	Meningitis	Necroses in spleen; infarcts in lungs	Only gross pathologic examination made
11	Bryant and Hirsch.....	M	W	48	Rabbit	16	Meningitis	Multiple lesions in liver, lungs, spleen, lymph nodes, leptomeninges, epidyma and choroid plexus	
12	Pernar and Macaehlan.....	M	N	36	Rabbit	17	Terminal pneumonia	Lesions in liver, lungs and lymph nodes	
13	Hartman.....	M	W	?	Rabbit	37	Encephalitis	Lesions in liver, lungs, spleen, lymph nodes and brain; none in meninges	
14	Foulger, Glazer and Foshay	F	W	37	Rabbit	22	Bronchopneumonia	Lesions in liver, lungs, spleen, lymph nodes and serosa of gastrointestinal tract	Treated with convalescent serum
15	Blackford.....	M	N	38	Opossum	37	Abscess of the lung	Lesions in lungs, lymph nodes and liver	
16	Hartman, Beaver and Green	M	W	62	Rabbit	18	Generalized infection	Lesions in lungs, liver, spleen and lymph nodes	Diagnosed ten years after death
17	Gudger.....	M	W	32	Rabbit	31	Bronchopneumonia	Lesions in lungs and lymph nodes	
18	Gundry and Warner.....	M	W	53	Rabbit	17	Pneumonia	Lesions in lungs, liver, spleen and lymph nodes	
19	Bernstein.....	F	W	53	?	24	Bronchopneumonia	Lesions in lungs, liver, spleen and lymph nodes	Not diagnosed clinically
20	Bernstein.....	M	N	55	Rabbit	20	Bronchopneumonia	Lesions in lungs, liver, spleen and lymph nodes	
21	Bernstein.....	M	W	52	Rabbit	19	Bronchopneumonia	Lesions in lungs, liver, spleen, lymph nodes and tonsils	

case of a man who died sixteen days after injuring a finger while skinning a wild rabbit. Recent authors emphasize the frequency of pulmonary complications in the fatal cases of tularemia. The patient observed by Goodpasture and House,⁴ however, gave no clinical signs of disease of the lungs. Similarly, in the case recounted by Palmer and Hansmann⁵ there was no evidence of pulmonary involvement. Simpson's⁶ patient died in less than five days after the onset of the disease—the most fulminant course yet reported. A physician, the history of whose illness was recorded by Bunker and Smith,⁷ had terminal bronchopneumonia and pulmonary edema. Pneumonia, likewise, was the final event in the instance of a worker in Georgian produce markets whose case was reported by Massee.⁸ Meningeal symptoms were the outstanding phenomena in the case reported by Haizlip and O'Neil.⁹ The cerebrospinal fluid contained 2,100 cells per cubic millimeter. Bryant and Hirsch's¹⁰ patient also presented the clinical picture of meningitis. There were 400 cells per cubic millimeter in the spinal fluid. Permar and Maclachlan¹¹ stressed the grave prognosis of that form of tularemia which is associated with diffuse pulmonary involvement, illustrating the assertion by their case. A third example of involvement of the central nervous system was reported by Hartman.¹² There were numerous focal necroses in the brain as well as evidence of meningitis. Foulger, Glazer and Foshay¹³ described tularemic lesions in which *Bacillus tularensis* was demonstrated in stained sections. Blackford¹⁴ recorded a fatal case in which the source of contagion was an opossum. Hartman, Beaver and

4. Goodpasture, E. W., and House, S. J.: The Pathologic Anatomy of Tularemia in Man, *Am. J. Path.* **4**:213, 1928.

5. Palmer, H. D., and Hansmann, G. H.: Tularemia: Report of a Fulminating Case with Necropsy, *J. A. M. A.* **91**:236 (July 28) 1928.

6. Simpson, W. M.: Tularemia; Study of Rapidly Fatal Case (Four Days, Seven Hours), *Arch. Path.* **6**:553 (Oct.) 1928.

7. Bunker, C. W. O., and Smith, E. E.: Tularemia; Report of Four cases, One Fatal, with Autopsy Report, *U. S. Nav. M. Bull.* **26**:901, 1928.

8. Massee, J. C.: Tularemia in Georgia; Report of a Fatal Case, *J. M. A. Georgia* **20**:66, 1931.

9. Haizlip, J. O., and O'Neil, A. E.: A Case of Meningitis Due to *Bacterium Tularensis*, *J. A. M. A.* **97**:704 (Sept. 5) 1931.

10. Bryant, A. R., and Hirsch, E. F.: Tularemic Leptomeningitis; Report of a Case, *Arch. Path.* **12**:917 (Dec.) 1931.

11. Permar, H. H., and Maclachlan, W. W. G.: Tularemic Pneumonia, *Ann. Int. Med.* **5**:687, 1931.

12. Hartman, F. W.: Tularemic Encephalitis, *Am. J. Path.* **8**:57, 1932.

13. Foulger, M.; Glazer, A. M., and Foshay, L.: Tularemia; Report of a Case with Postmortem Observations and a Note on the Staining of *Bacterium Tularensis* in Tissue Section, *J. A. M. A.* **98**:951 (March 19) 1932.

14. Blackford, S. D.: Pulmonary Lesions in Human Tularemia; Pathologic Review and Report of a Fatal Case, *Ann. Int. Med.* **5**:1421, 1932.

Green¹⁵ reported a case of tularemia which occurred in Minnesota in 1921 but which was diagnosed only in retrospect after an interval of ten years. This probably is the earliest fatal case concerning which pathologic information is recorded in the American literature. Gudger¹⁶ reported the case of a person with extensive areas of pulmonary consolidation in the absence of peripheral glandular enlargement. The most recent instance of fatal tularemia is that described by Gundry and Warner.¹⁷

REPORT OF CASES

CASE 1.¹⁸—M. E. G., a 53 year old white widow, was admitted to the Johns Hopkins Hospital on Dec. 8, 1930, complaining of vomiting and fever of twelve days' duration. There was a history of twelve operations: a hysterectomy and bilateral salpingo-oophorectomy, excision of a subsequent sinus tract, cholecystectomy and nine attempted repairs of a ventral hernia. The last operation had been performed in June 1930, at which time a general physical examination revealed nothing of note aside from the abdominal condition except moderate arteriosclerosis and a blood pressure of 200 systolic and 100 diastolic. The patient kept a boarding house in Baltimore and had not recently been out of the city.

Twelve days before admission, while cooking dinner, she suddenly fell to the floor, faint but not unconscious. A shaking chill lasting an hour followed, with continuous nausea and vomiting. Fever continued high for twelve days with constant vomiting so that she was unable to retain even water. Six days before entry her mouth and tongue became sore. Constipation was marked during the present illness.

On admission the temperature was 103.8 F., the pulse rate 94, the respiratory rate 18 and the blood pressure 148 systolic and 80 diastolic. She was moderately well nourished, acutely ill, and apathetic. The skin was dry. There was one questionable rose spot on the abdomen, and eczematous lesions were present over the buttocks. There was no pallor or cyanosis. There was no general glandular enlargement. The pupils reacted normally to light. The lips were dry. The tongue was heavily coated and the pharynx somewhat injected. The lungs were clear. The heart was not enlarged and was normal to auscultation. There was no abdominal distention. The liver and spleen were not palpable. Examination of the extremities and neurologic examination gave no remarkable results.

After admission the patient's progress was steadily downward. She continued to vomit, took fluids poorly and became progressively weaker. The temperature ranged from 102 to 105 F., with a terminal rise to 107.4 F. The striking developments were extreme cyanosis, which antedated and seemed much out of proportion

15. Hartman, H. R.; Beaver, D. C., and Green, R. G.: The Occurrence of Tularemia in Minnesota in 1921: Report of Two Cases—One Fatal with Necropsy Report, *Minnesota Med.* **16**:559, 1933.

16. Gudger, J. R.: Tularemic Pneumonia; Report of a Case, *J. A. M. A.* **101**: 1148 (Oct. 7) 1933.

17. Gundry, L. P., and Warner, C. G.: Fatal Tularemia: Review of Autopsied Cases with Report of a Fatal Case, *Ann. Int. Med.* **7**:837, 1934.

18. This case has been reported briefly by Hamman, L.: Clinical-Pathological Conference: A Case of Severe Anemia with Cardiac Manifestations; A Case of Obscure Infection, *South. M. J.* **26**:665, 1933.

to the signs of bilateral bronchopneumonia that appeared a week after entry, dyspnea without evidence of myocardial failure and an utter lack of localizing signs for what was clearly an overwhelming infection. On December 20, twenty-four days after the onset of the illness, the patient died of exhaustion.

Laboratory Data.—The results of blood counts were as follows:

	Hemo- globin, per Cent	Red Cells	White Cells	Polymorpho- nuclears, per Cent	Lympho- cytes, per Cent	Mono- nuclears, per Cent
12/ 8/30	90	5,740,000	9,720	72	18	10
12/ 9/30	10,760
12/10/30	12,120
12/11/30	86	4,280,000	18,000	79	19	2
12/14/30	75	3,910,000	12,050	87	8	5
12/18/30	66	3,820,000	14,200	88	7	5

The result of the Wassermann test on December 10 was negative; that of the flocculation test, doubtful. Chemical examination of the blood on December 20 showed: nonprotein nitrogen, 41 mg. per hundred cubic centimeters of blood; van den Bergh test, negative. Cultures of the blood on December 8, 9, 11, 12, 17 and 20 showed no growth. Cultures of the stools repeatedly gave negative results for the typhoid-dysentery group of bacilli but always showed occult blood. Examination of the urine revealed albumin (+), no sugar and occasional white blood cells. A culture was sterile. Agglutination tests gave the following results:

Agglutinations	Test	Results
Dec. 8, 1930.....	Widal	Negative
Dec. 10, 1930.....	Widal	Negative
Dec. 11, 1930.....	Widal	Negative
Dec. 12, 1930.....	Widal	Negative
Dec. 16, 1930.....	Widal	Negative
Dec. 17, 1930.....	For B. melitensis Weil-Felix	Negative Negative

On June 18, 1930 (previous admission) the teleoroentgenographic measurements were median right 3.5, median left 9.6, and thoracic 26.1 cm. Roentgen examination of the chest showed the lungs clear and the heart and aorta within normal limits. On December 10 and 12 (present admission) the lungs were clear. On December 18 there was evidence of bronchopneumonia in the left lung.

The pulse rate varied from 90 to 130 and the respiratory rate from 24 to 50; the blood pressure, which was low on entry, rose to 218 systolic and 75 diastolic at the end.

The clinical diagnosis was miliary tuberculosis (?), typhoid (?) and bronchopneumonia.

Autopsy.—The autopsy was performed twenty-one hours after death by Dr. F. B. Kindell.

Macroscopic Examination: The body was that of a well nourished middle-aged white woman. There was rigor mortis of the extremities. The scleras were pale. There was slight edema of the ankles. A long scar was present in the midline of the abdomen. The rectus muscles were separated about 3 cm., but there was no hernial pouch.

There were adhesions about the gallbladder and between the intestine and the abdominal wall near the scar of the operative incision. There were dense adhesions about the site of the hysterectomy. There was no free fluid in the abdominal cavity.

The left pleural cavity contained 150 cc. of bloody fluid. The posterior and inferior pleural surfaces were covered by a fibrinopurulent exudate with numerous areas of hemorrhage. There were no old adhesions. There was no free fluid in the right pleural cavity. Over the lower lobe of the right lung there was a fibrinopurulent exudate like that on the left. The pericardial cavity was normal.

The heart weighed 320 Gm. The epicardium was smooth. The auricles contained no thrombi. All the valves were normal. The myocardium showed no gross scars. The coronary arteries were patent. They showed only slight arteriosclerosis.

The lungs were for the most part air-containing. The pleural surfaces of the upper lobes were smooth. There were no apical scars. The posterior and lateral



Fig. 1 (case 1).—Macroscopic view of the lungs, showing caseous glands at the hilus and fibrinous pleurisy. (The photographs shown in figures 1 to 6 were made by Mr. Milton Kougl.)

surfaces of both lower lobes were covered by a layer of edematous yellow fibrin, in places from 2 to 3 mm. in thickness. The pleural surfaces were dull and granular with numerous flecks of hemorrhage. Scattered gray nodules could be seen beneath the pleura. On scraping away the surface layer of fibrin, very tiny granules could be seen, suggesting tubercles.

On section the lower lobes of both lungs contained scattered tubercle-like nodules. Often these attained a size from 5 to 6 mm. and were made up of groups of confluent smaller nodules. There were a few larger patches of gray consolidation suggesting those seen in caseous pneumonia. One such firm area measured 3 cm. in width. It occupied the posterior upper part of the left lower

lobe and came to the pleural surface. The rest of the tissue of this lobe was red, soft and elastic. The upper lobes were more distended with air and gray-pink. Only an occasional tubercle-like nodule was seen on the cut surface.

The peribronchial nodes were enlarged. Two or three were caseous and softened. One at the hilus of the left lung was 2.5 cm. in diameter. It contained a central firm nodule from 5 to 6 mm. in diameter, which was hyaline and pigmented, suggesting an old scarred lesion. The peripheral portion of the node was white and caseous, and in part the material was soft and semifluid. Other nodes showed good-sized peripheral caseous masses.

The spleen weighed 320 Gm. It was enlarged and soft. The delicate capsule tore readily. The surface was dull and finely granular. On section the surface was studded with gray or yellowish nodules varying in size up to 4 and 5 mm.

The mucosa of the intestines showed no lesions. No ulcers or source of hemorrhage was found. The colon was the site of a number of small diverticula. The mesenteric nodes were not enlarged, and no caseous nodules were found.

There were scattered punctate hemorrhages in the gastric mucosa, but no gross ulcers. The mucosa of the duodenum was normal.

The pancreas was normal.

The liver weighed 1,600 Gm. The capsule was smooth. The liver was softer than usual. On section the lobulation was accentuated. The center of each lobule contained a yellow opaque fleck, or in other places a red spot, while the periphery was paler red-brown with a slight yellowish tinge. There were numerous scattered nodules, often 2 mm. in diameter.

The gallbladder contained eight stones, which were very much alike in size and shape, measuring 12 by 12 by 15 mm. as a rough average. They were pyramidal, with concave surfaces and smaller facets near the corners. The wall of the gallbladder was not thickened. No stones were found in the bile ducts, which were not distended.

The adrenal glands and kidneys were normal.

The bladder was tied down by adhesions and was normally adherent to the pelvis. Its wall was thin, and the mucosa showed no lesions. The cervix of the uterus was all that remained. There were no remarkable findings on section.

The pharynx and larynx were normal. The thyroid gland was not enlarged and was normal on section. Two caseous nodes were found near the bifurcation of the trachea.

The aorta showed considerable arteriosclerosis. There were elevated plaques about the intercostal arteries. The thoracic aorta showed much more longitudinal wrinkling of the intima than usual, which in one or two places became a radiate pucker suggesting aortitis, but there was no other evidence to support this.

The bone marrow of the femur contained rather large islands of red hyperplastic tissue.

One large caseous node at the hilus of the liver measured 3.5 by 2 cm. This one on section was completely caseous, and the contents were in part soft and viscous. A second smaller node, 1.5 cm. in diameter, which was also caseous and soft, was found near the pancreas. No other caseous abdominal lymph nodes were found. A small node, 1 cm. in diameter, was found near the aorta behind the pleura. No grouping of nodes about the thoracic duct was present to suggest a lesion there, and the duct itself was normal in appearance.

Microscopic Examination: Study of the heart showed that the muscle fibers were atrophic, many of the cells contained more pigment than usual, and there were more nuclei and cells in the interstitial tissue than usual.

Three sections of the lungs showed an organizing fibrinous or fibrinopurulent pleurisy. There was a rather fresh lesion which was quite like that seen in tuberculous lobular pneumonia, with fresh necrosis and caseation. Many of the areas were rather compact and hyaline. No tubercle bacilli were seen in stains of these sections. One of the sections showed the two older caseous nodules in the lower lobe of the left lung. In the center these were hyaline and pigmented but still not extremely old. There seemed to be a spread of these lesions with a fresher process in the periphery. No tubercle bacilli or other bacteria were found on careful search.

In the spleen there were a few caseous nodules with fragmented material in the center and narrow hyaline capsules. No tubercle bacilli or other bacteria were found in the lesions on most careful staining and search.

There was rather marked atrophy of the central liver cells, and an occasional necrotic cell was seen. There were a few caseous areas, which showed beginning encapsulation. No bacteria were revealed by any stain.

The tubular epithelium of the kidneys was ragged and granular.

In the aorta there was arteriosclerosis but nothing to suggest syphilis.

One section made of the lymph nodes was from a bronchial node. The other two showed the softened nodes at the hilus of the liver. The first contained an older, quite hyaline lesion. All showed fresh caseation, and one showed a caseous lesion extending into the surrounding fat. Smears from these nodes showed no tubercle bacilli, even after concentration with sodium hydroxide. No other bacteria were found.

The bone marrow of the femur showed considerable hyperplasia.

Further stains for bacteria, including stains for tubercle bacilli and Nicolle's tannic acid-methylene blue stain for glanders, failed to show any organisms.

A summary of Dr. MacCallum's notes is as follows: The lungs, liver, lymph nodes and spleen showed areas which at first sight looked like an acute tuberculous necrotizing process. No actual tubercles were seen, however, and no lesions which might be regarded as typically tuberculous. Above all, no tubercle bacilli were found after the most careful staining and search.

Bacteriologic Studies.—A smear of the heart blood showed no organisms. From a culture no organisms resembling *B. tularensis* were grown.

A guinea-pig inoculated in the groin with material from an abdominal lymph node did not die. However, the gland had been kept in the icebox for a period preceding the inoculation.

Anatomic Diagnosis.—The diagnosis was: tularemia; caseous lobular pneumonia; bilateral pleurisy (fibrinopurulent); caseous peribronchial and peritracheal lymph nodes; large caseous lymph nodes at the hilus of the liver and near the pancreas; caseous foci in the liver and spleen; cholelithiasis; peritoneal adhesions; evidence of a hysterectomy; diverticula of the colon; areas of encephalomalacia and calcified vessels in the globus pallidus.

CASE 2.¹⁹—F. P., a 55 year old Negro laborer, was admitted to the Johns Hopkins Hospital on Dec. 31, 1931, complaining of shortness of breath, chills and fever. The patient's condition was such that a satisfactory history was never obtained from him, but apparently his general health had been excellent in the past. He had suffered from occasional headaches and from nocturia (urinating two or three times a night) for several years. His recent work had been that of a day laborer on a farm.

19. The history is given here in the manner in which the details were divulged rather than in the true chronological order.

Two weeks before admission he contracted a cold and cough, which were severe enough to prevent him from working but did not cause him to go to bed. Four days later he had a chill. Breathing became difficult. Eight days before entry the urine became "black," and it remained so until the day before admission, when it became reddish. Three days before, the cough became productive of yellowish sputum. The patient now went to bed. On the following day he complained of dizziness and had bouts of delirium. During the two weeks before admission he vomited only once and probably had some fever, but no sweats.

On admission the temperature was 102.2 F., the pulse rate 124, the respiratory rate 44 and the blood pressure 130 systolic and 80 diastolic. He was acutely ill, delirious and disoriented. There was marked cyanosis, with rapid, shallow respirations. He had an occasional unproductive cough. There was questionable stiffness of the neck. The tongue was coated. The throat could not be examined. The epitrochlear glands were palpable, but the other peripheral lymph nodes were not enlarged. The lungs showed impairment of the percussion note below the angle of the scapula on the left, with suppression of breath sounds over the same area. In both axillae there were many fine moist râles. The heart did not seem enlarged. The sounds were somewhat obscured by pulmonary noises. There was a progression of arrhythmia, bigeminy, pulsus paradoxus and auricular fibrillation following closely on one another. The abdomen was moderately distended. The liver was enlarged 2 fingerbreadths to percussion, but the edge was not felt. The spleen was not felt. Neurologic examination gave no remarkable results aside from a possible Kernig sign.

On the day after admission the patient appeared somewhat improved. The symptoms were still predominantly pulmonary. The condition in the chest had changed little save that the breath sounds showed more prolongation of expiration over the lower lobe of the left lung. A lumbar puncture yielded normal spinal fluid. The fever ranged between 103 and 105 F. The situation was essentially the same on the following day. There were diffuse pulmonary signs without definite evidence of consolidation. Delirium continued. At this time it was discovered that the right epitrochlear gland had become enlarged to a diameter of 3 cm. Further investigation disclosed an apparently healed lesion on the ball of the right thumb, which, however, was tender to pressure. Further questioning of the patient's family yielded the information that one week before the onset of the present illness he had skinned and cleaned three or four rabbits, during which process he had pierced his right thumb with a bone. Subsequently the thumb had become sore, so that on two occasions during the first week of his illness it had been punctured with a needle by the patient's sister and pus had been obtained. With this new guide, further tests were carried out, and the patient's serum was found to agglutinate the tularemia antigen. From then on he became rapidly worse. He sank into coma and showed progressive signs of intoxication. Generalized râles developed in the lungs, and purulent conjunctivitis of the right eye appeared. Cyanosis was extreme, the cardiac arrhythmia continued, and he died on Jan. 5, 1932, the twentieth day after the onset of the acute illness.

Laboratory Data.—The results of blood counts were as follows:

	Hemo- globin, per Cent	Red Cells	White Cells	Polymorpho- nuclears, per Cent	Lympho- cytes, per Cent	Mono- nuclears, per Cent
12/31/31	88	4,230,000	6,880	27	61	12
1/ 1/32	4,280
1/ 2/32	4,920
1/ 3/32	5,120
1/ 4/32	5,920	76	22	2

The Wassermann reaction on January 1 was negative; the flocculation test gave negative results.

Examination of the cerebrospinal fluid showed 1 cell per cubic millimeter. The Pandy and Wassermann reactions were negative.

Chemical examination of the blood on January 2 showed nonprotein nitrogen, 50 mg. per hundred cubic centimeters, and carbon dioxide-combining power, 42.8 volumes per cent; on January 4, nonprotein nitrogen, 69 mg. per hundred cubic centimeters, and carbon dioxide-combining power, 43.8 volumes per cent.

Cultures of the blood on Dec. 31, 1931, and on Jan. 2, 1932, showed no growth.

A smear showed that the sputum did not contain tubercle bacilli. A culture revealed *Staphylococcus aureus* and beta hemolytic streptococci.

The urine was reddish and contained albumin (++) , no sugar and occasional white blood cells. Spectroscopic examination showed hemoglobin to be present (the benzidine reaction was negative). The results of agglutination tests were as follows:

Agglutinations	Test	Results
Jan. 2, 1932.....	Widal For <i>B. tularensis</i>	Negative Positive, 1:160 (dilution carried no higher)
Jan. 4, 1932.....	For <i>B. melitensis</i>	Negative

Material from lesions, glands and blood was examined. On January 3 a smear was made of pus from the right thumb, but the results were negative. Pus was taken from a gland in the right epitrochlear region for a smear, which showed suspicious gram-negative bacilli. A culture produced no growth. A guinea-pig given an injection of blood taken from the patient died in two days. Autopsy showed multiple necroses in the liver and spleen.

An electrocardiogram made on January 4 showed normal sinus rhythm, sinus tachycardia and an upright T wave in all leads.

On December 31 roentgenograms of the chest revealed diffuse infiltration of both lungs, possibly bronchopneumonia; on January 2 small areas of bronchopneumonia and the mediastinal shadow enlarged owing to dilatation of the aorta.

The pulse rate varied from 48 to 160; the respiratory rate, from 24 to 52, and the temperature, from 102.2 to 105.6 F.

The clinical diagnosis was tularemia, bronchopneumonia and arteriosclerosis.

Autopsy.—The autopsy was performed four hours after death by Dr. G. Fite.

Macroscopic Examination: The body was that of a well nourished Negro of middle age. There was moderate rigor mortis. The head, eyes and ears were normal. There was no edema. There were no cutaneous lesions except an incised wound on the ball of the right thumb, exuding a little necrotic material. A large lymph node lying just above the elbow had been punctured by a needle.

Both pleural cavities contained a little fibrinous exudate, most of which was plastered on the surfaces of the lungs. There was no fluid. There were numerous small hemorrhages.

The heart weighed 360 Gm. The right auricle seemed quite large. The right ventricle was not particularly hypertrophied, although it might be somewhat dilated. The pulmonary valve was normal, and so was the mitral valve. There were minute grayish opacities here and there in the musculature of the left ventricle, and the endocardium was thickened throughout. The aortic valve was normal.

The pleural surfaces of the lungs were flecked with fibrin. There were scattered areas, sometimes quite large, of lobular pneumonia. The bronchi were reddened and roughened. Some of the areas of lobular pneumonia were small and

sharply outlined and on the cut surface had a smooth, uniformly gray appearance. The lymph nodes at the hilus were not particularly enlarged. One of them showed old gray scars suggesting tuberculosis.

The liver was large, weighing 1,900 Gm. Scattered through it one could see a few sharply outlined gray or yellowish-gray nodules, 1 or 2 mm. in diameter. On careful inspection these seemed to be numerous. The centers of the lobules in many places appeared to contain more blood than was normal. The capsule of the liver was smooth.

The spleen was considerably enlarged, weighing 500 Gm. Its surface was studded with myriads of small caseous nodules similar to those in the liver. Beneath the capsule one could see many white and yellowish-gray areas varying in size from a pin point to 6 or 7 mm. in diameter, and on section these areas were plainly seen on the cut surface, studding the organ almost uniformly throughout.

The kidneys were normal in size. The capsule came away, leaving a perfectly smooth surface, and on section the architecture appeared normal.

The pancreas was normal. The lymph nodes about the pancreas were large and contained gray nodules.

The adrenal glands were large. They had a very darkly pigmented zone outside the medulla.

There was an ulceration in the esophagus just at the region of the bifurcation of the trachea. This was about 1 by 0.5 cm., was rather sharply outlined and had a greenish base. There were roughening and reddening of the trachea at the bifurcation, and a diphtheritic-like exudate covered the surface. It was not ulcerated, and the ulcer in the esophagus was not related to any lesion in the underlying trachea.

The aorta was somewhat sclerotic.

The large epitrochlear lymph node on the right side on section contained a large abscess, measuring about 1 cm. in diameter. There were in it also numerous small caseous nodules. The large lymph nodes in the axilla on the right side had much the same appearance. Several of them contained caseous areas. A few of them had the appearance of abscesses. The lymph nodes in the left axilla and in both groins were not altered, except for one scarred and pigmented node in the right inguinal region.

There were large lymph nodes about the bifurcation of the trachea. These were anthracotic and had gray flecks and streaks through them, suggesting an old tuberculous process. On the right side of the neck just below the thyroid gland there was a very large mass of anthracotic lymph nodes which were flecked throughout with gray. This mass measured about 7 cm. in length and lay just lateral to the trachea. The lymph nodes were all separate from each other, and higher up there were still others, enlarged, anthracotic and flecked with gray, which were rather firm. On the opposite side, there were some small lymph nodes which had the same general character. On one side there was a fairly large hilar lymph node of the same character.

The bone marrow of the femur was fatty. There were small yellow opacities in the bone marrow of the vertebrae. The meninges were rather cloudy over the surface of the brain and, indeed, over the temporal lobes as well. This did not appear to be a fresh exudate of any sort but rather resembled a thickening of the meninges themselves. There was perhaps slight atrophy of some of the convolutions. The brain was normal in several sections.

Microscopic Examination: The lesions characteristic of tularemia were seen abundantly in the lungs, liver and spleen and in lymph nodes from all regions of the body. They closely resembled very soft caseous tubercles, with necrotic

centers filled with débris and surrounded by margins of better preserved mononuclear cells. There were a good many polymorphonuclear leukocytes about some of the foci, especially in the spleen. These were exceedingly numerous in the spleen and were of quite irregular pattern and variable in size. Giant cells were rarely found. Only one was seen in the spleen. The distribution of the lesions apparently bore no relation to the anatomic structure in any organ. In the epitrochlear lymph nodes, the lesions had coalesced to form a fairly large abscess.

In the skin of the thumb, the same sort of lesion was seen, with many mononuclear cells.



Fig. 2 (case 2).—Mass of caseous anthracotic lymph nodes about the aorta.

The lungs showed beautifully the lesions of tularemia, with areas of necrotic pneumonia, which resembled tuberculous caseous pneumonia very closely, except that they did not in any way suggest distribution by aspiration, and the lesion destroyed the lung tissue throughout its extent. Closely mingled with these lesions were areas of lobular pneumonia due to the pneumococcus (type II) which was seen in abundance in bacterial stains.

No *Bacilli tularensis* were stained in the section in spite of many diverse attempts both on tissue fixed in formaldehyde and Zenker's solution and on frozen sections.

Bacteriologic Studies.—A smear of the heart blood showed no organisms, and a culture was sterile. A smear of material from the spleen showed no organisms, and a culture was sterile. A culture of lung tissue showed pneumococcus (type II).

Anatomic Diagnosis.—The diagnosis was as follows: tularemia; a necrotic wound in the right thumb; caseous nodules and abscesses in the right epitrochlear and the axillary lymph nodes; caseous miliary nodules in the spleen and liver; extensive caseous lobular pneumonia; acute fibrinous pleurisy, and hemorrhages in the pleura.

CASE 3.—T. B. F., a 52 year old white man, a nail inspector, was admitted to the Johns Hopkins Hospital on Dec. 1, 1932, complaining of chills and fever. His past health had always been excellent. Two and a half weeks before, he shot and skinned a wild rabbit. At the time there was an unhealed cut from an accidental injury on his right thumb. Three days later he was seized with a chilly sensation, and anorexia developed. Nine days before admission he became weak and feverish. Four days later, he was compelled to go to bed, when drowsiness and apathy were striking. Three days before admission, frontal headache appeared along with a sore throat and increasing constipation. His temperature was found to be 103 F. From then on he became rapidly weaker and was almost constantly delirious.

On admission his temperature was 104 F., the pulse rate 130, the respiratory rate, 30, and blood pressure 120 systolic and 65 diastolic. He was a large man, acutely ill, delirious and uncooperative. There was extreme cyanosis of the mucous membranes, as well as great dyspnea and orthopnea. He was sweating profusely. The scar of a cut on the ball of the right thumb was incompletely healed. There were no palpable glands save in the left cervical chain. His tongue was very red and deeply fissured. There were patches of grayish exudate with a hemorrhagic base on the soft palate. Breathing was labored but regular. There was moderate emphysema. Both lungs were filled with moist râles without any definite evidence of consolidation. The pulse was rapid. The heart sounds were obscured. There was a loud apical systolic murmur. Marked abdominal distention was present. The liver and spleen were not palpable. There was slight edema of the ankles. The neurologic examination gave negative results.

The use of an oxygen tent gave some relief. However, all of the symptoms present on entry persisted, while the patient became rapidly more prostrated. Distention was combated with difficulty. He was unable to void. There was an occasional unproductive cough. Several days after admission a pustule developed at the center of the lesion on the thumb. At the same time an enlarged gland was felt in the right axilla. Subsequently this became larger and fluctuant. With increasing tachycardia, unabated dyspnea and cyanosis and continued sweats, the patient died on Dec. 5, 1932, nineteen days after the onset of his illness.

Laboratory Data.—The results of blood counts were as follows:

	Hemo- globin, per Cent	Red Cells	White Cells	Polymorpho- nuclears, per Cent	Lympho- cytes, per Cent	Mono- nuclears, per Cent
12/1/32	86	4,000,000	10,250	80	20	..
12/2/32	9,600
12/3/32	7,300	81	17	2
12/4/32	3,550	75	21	4

The Wassermann reaction on December 1 was negative. The flocculation test gave negative results. Chemical examination of the blood on December 3 showed

36 mg. of nonprotein nitrogen per hundred cubic centimeters of blood. The van den Bergh indirect test showed a faint trace.

Cultures of the blood on December 1 and 3 showed no growth.

A culture of the stools gave negative results for the typhoid-dysentery group of bacilli. The guaiac test gave a positive reaction.

The urine contained: albumin $++$, no sugar and occasional white blood cells and granular casts. A culture showed no growth. The results of agglutination tests were as follows:

Agglutinations	Test	Results
Dec. 1, 1932.....	Widal	Negative
	For <i>B. tularensis</i>	Positive, 1:80
Dec. 2, 1932.....	For <i>B. melitensis</i>	Negative
Dec. 3, 1932.....	For <i>B. tularensis</i>	Positive, 1:160
Dec. 4, 1932.....	For <i>B. tularensis</i>	Positive, 1:320

A guinea-pig given an injection of the patient's blood on December 2 died in two days. Autopsy showed multiple focal necrotic lesions in the spleen and liver.

On December 2, also, roentgenograms of the chest showed both lungs extensively solidified.

The pulse rate varied from 130 to 180; the respiratory rate, from 24 to 42, and the temperature, from 99 to 104.2 F.

The clinical diagnosis was tularemia and pneumonia.

Autopsy.—The autopsy was performed three hours after death by Dr. E. Henriksen.

Macroscopic Examination: The body was that of a well nourished, well developed white man. There was very slight rigor mortis. On the right thumb there was a well healed scar near the tip.

There was no free fluid in the abdominal cavity. The peritoneal surfaces were smooth.

There was no free fluid in either pleural cavity. The pleural surfaces were rough and covered with a fibrinopurulent exudate, more marked at the base of the right lung. There were fine adhesions over the entire lateral and posterior aspects of both lungs.

The heart weighed 425 Gm. The endocardium and myocardium appeared normal. The valves were all essentially normal, except for the aortic valve, in which there was slight thickening of the border of each cusp. There was a moderate degree of arteriosclerosis of the aorta and its branches.

The lungs were bulky. There was a whitish layer of fibrin on the posterior surface of the lower lobe of the right lung. The whole pleural surface was dull and granular, with good-sized patches in which hemorrhage had occurred. White areas shone through the pleura and stood out above the surface.

On section there were large white opaque areas of consolidation. These stood out on the cut surface and were very sharply outlined, with areas of hemorrhage about some of them. They were so opaque as to suggest caseous lesions. The swollen peribronchial lymph nodes contained white caseous areas. The bronchi were reddened and roughened. There were in addition to these lesions, edematous, reddish, softer pneumonic areas.

The spleen weighed 125 Gm. The capsule was wrinkled, and there were numerous small gray flecks sprinkled over the entire surface. On section the pulp was soft, dark and purplish red, with several small necrotic nodules scattered through it.

The intestines were normal.

The pancreas was normal.

The liver was somewhat enlarged, weighing 2,100 Gm. The lobulation was accentuated. On the cut surface, sharply outlined small opaque nodules could be seen. They resembled small tubercles, some of them being almost 1 mm. in diameter.

Together the adrenal glands weighed less than 5 Gm. On section the medulla was gelatinous. The cortex, however, was well outlined.



Fig. 3 (case 3).—Large areas of caseous consolidation as well as fibrinous pleurisy in a lung.

The kidneys were normal in size. The capsules stripped easily. The kidney substance appeared normal.

The trachea and larynx were normal. There was some enlargement of the cervical lymph nodes, more marked on the right side. On section these were found to contain small abscesses, filled with grayish pus.

From the right axilla two large lymph nodes were removed. One was about 2 cm. in diameter. On section these were found to be partially necrotic.

The bone marrow of the femur was red and jelly-like. The vertebral bone marrow appeared normal.

Microscopic Examination: Sections from the heart were normal. Sections were made of bronchial and axillary lymph nodes. One section showed an enlarged node, with several abscess cavities present. These were filled with a grayish-yellow pus at autopsy. About the cavities there were areas of caseous necrosis and infiltration of the tissue with polymorphonuclear and epithelioid cells and other mononuclear cells. Scattered throughout the gland were numerous caseous areas. No giant cells were found. No tubercle bacilli or other bacteria were found in appropriately stained sections.

In some sections of the lungs marked caseous pneumonia was shown. In others the alveoli were distended with polymorphonuclear leukocytes. There was no interstitial pneumonia. About some of the caseous areas epithelioid cells were found, but there were no giant cells. Careful study failed to reveal any inclusion bodies. Various bacterial stains, including Nile blue, failed to demonstrate *B. tularensis*, and no tubercle bacilli were found.

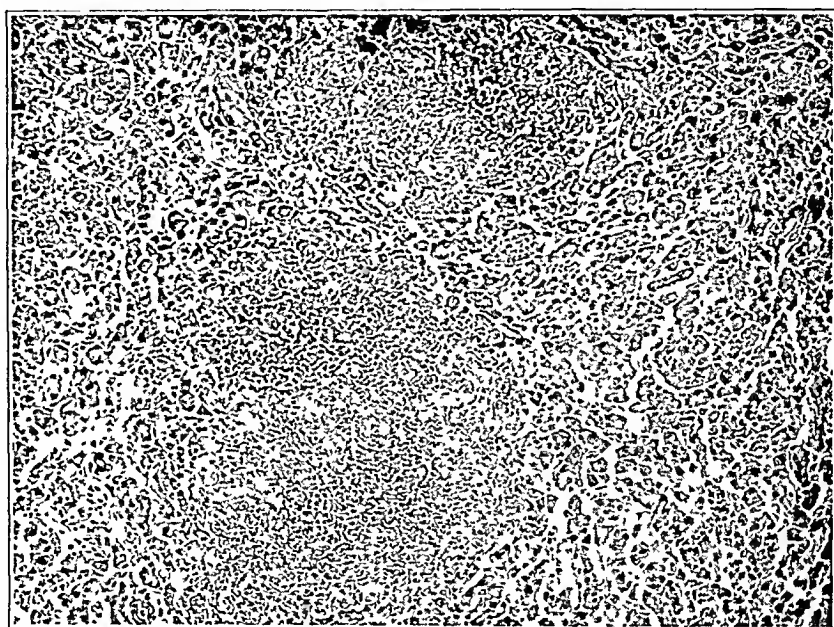


Fig. 4 (case 3).—Photomicrograph of the liver, showing areas of focal necrosis.

Scattered throughout the liver substance were numerous small caseous areas, not unlike tubercles. They had caseous centers with large epithelioid cells but no giant cells. These areas did not seem to bear any relation to the lobule, being both periportally and centrally located. Several of the periportal spaces showed a marked increase in lymphocytes. No bacteria were seen, and there were no acid-fast organisms present.

Scattered throughout the splenic pulp were numerous areas in various stages of caseation, with definite necrotic centers and a few large epithelioid cells scattered about. There were no giant cells.

A section taken through the back of the tongue and one of the tonsils showed some scarring of the tonsil. In one of the crypts there was a large caseous area similar to those seen elsewhere.

Bacteriologic Studies.—A culture of the heart blood was sterile. A culture of material from the lung showed *Haemophilus influenzae* and *Pneumococcus* (type I).

Anatomic Diagnosis.—The diagnosis was as follows: tularemia; caseous areas in the lungs, liver, spleen, lymph nodes and tonsils; diffuse caseous pneumonia; lobular pneumonia; fibrinopurulent pleurisy; an acute splenic tumor; a recent scar on the right thumb; an encapsulated foreign body in the lesser curvature of the stomach, and arteriosclerosis.

COMMENT

Of the three cases reported, the first seems to fall into the typhoid group, while the second and third are examples of the ulceroglandular form of tularemia, in the last two cases the portal of entry being an injury on the thumb. Perhaps a more inclusive term for all three would be the pulmonic form. It is conceivable that a local lesion was neglected in the first instance, since no suspicion of the true nature of the disease was held during the life of the patient. In the two cases in which a history of exposure was elicited, the source of infection was a wild rabbit, the usual offender. For this reason, as has been pointed out by Francis, the majority of tularemic infections are encountered in November, December and January. In this instance all three patients were admitted to the hospital in December.

The present series included one white woman, one white man and one Negro. All three were in the early fifties. (No particular significance is attached to this fact since tularemia has occurred in persons between the ages of 2 and 70.)

In case 2 the injury preceded the onset of symptoms by one week; in case 3, by only three days. The duration of the disease was almost the same in all three cases, death occurring on the twenty-fourth, twentieth and nineteenth days of the acute illness, respectively.

The clinical pictures were not dissimilar. The patients were acutely ill on admission. The course was characterized by sustained fever, tachycardia, dyspnea, prostration, delirium, signs of intoxication, cyanosis (sometimes out of proportion to the objective pulmonary signs and always extreme), constipation and abdominal distention. In each case at some period of the stay in the hospital it was deemed advisable to employ digitalis. The oxygen tent was frequently resorted to in all three cases.

Previous authors have stressed the ominous import of evidences of pulmonary involvement in cases of tularemia. Their claims are amply borne out in the present cases, in which the lungs were affected to a greater or lesser degree. Characteristically the signs were diffuse, terminally extensive but without indisputable signs of consolidation. In these respects they simulated the picture of postinfluenzal interstitial pneumonia, a clinical entity with which advanced tularemia might readily be confused.

In the only case in which the hemoglobin was determined more than once, rapidly progressive anemia was noted (from 90 per cent to

66 per cent within ten days). In another case the patient had persistent hemoglobinuria. This same patient acquired conjunctivitis, which was apparently unrelated to the chief malady. No significant cutaneous eruptions were noted, nor was there definite evidence of meningeal involvement.

So far as laboratory findings were significant, only agglutinations of blood and inoculations of animals provided definite information. The white blood cell count ranged between 3,500 and 18,000, the results of a majority of the determinations falling within normal or slightly elevated limits. Leukocytosis, when present, was of a polymorphonuclear type. Blood cultures on plain and dextrose agar gave uniformly negative results. Agglutinations for *B. tularensis* gave positive results in

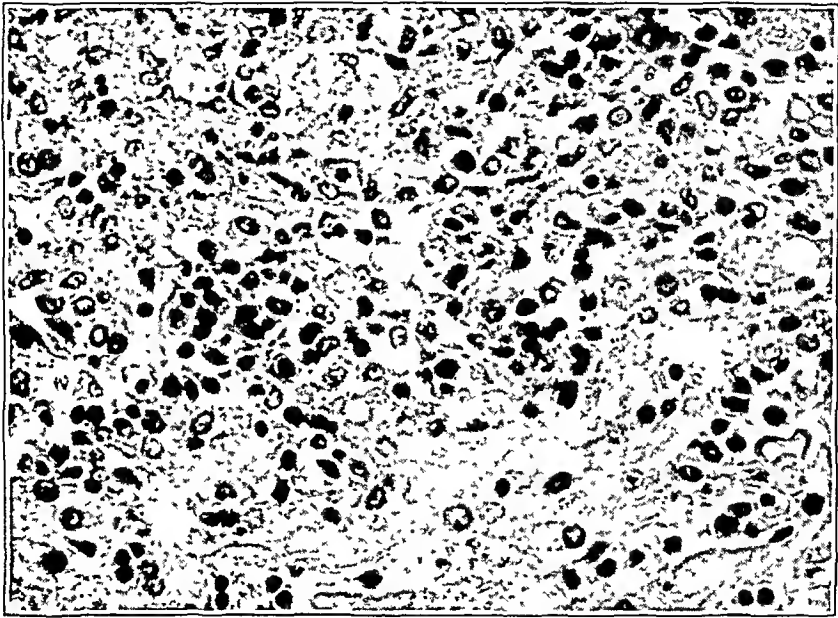


Fig. 5 (case 1).—Photomicrograph of the liver, showing the character of the cellular exudate at the periphery of a necrotic focus ($\times 400$).

the two cases in which they were made; in case 2 there was a titer of 1:160 on the seventeenth day of illness; in case 3, a titer of 1:320 on the eighteenth day. None of the three serums agglutinated *B. melitensis*, a phenomenon which is met with in 25 per cent of cases of tularemia. Intraperitoneal injections of blood collected from the last two patients on the eighteenth and sixteenth days of the illness, respectively, brought about rapid death to guinea-pigs, at the autopsies of which there were found characteristic focal necroses in the liver and spleen.

The pathologic changes were strikingly uniform in the three cases. In all there was involvement of lymph nodes, lungs, liver and spleen. In the last case there were definite changes in the tonsillar crypts. The

lesion of tularemia resembles the soft tubercle in many ways but differs from it in two notable respects: the absence of tubercle bacilli and the absence of giant cells. In the less necrotic areas, the caseous nodules contain mononuclear cells and often a great many polymorphonuclears.

The pleurae in all instances were involved in an acute fibrinopurulent process, frequently with hemorrhages. In the lungs there were areas caused by caseous pneumonia, as well as many smaller necrotic lesions. The liver was enlarged and soft in consistency. The caseous nodules were distributed without apparent relation to the hepatic structure. Likewise the spleen was soft and usually enlarged. The lesions here were more abundant than in the liver. Scattered lymph nodes about the body were enlarged. The glands draining a primary lesion, in an

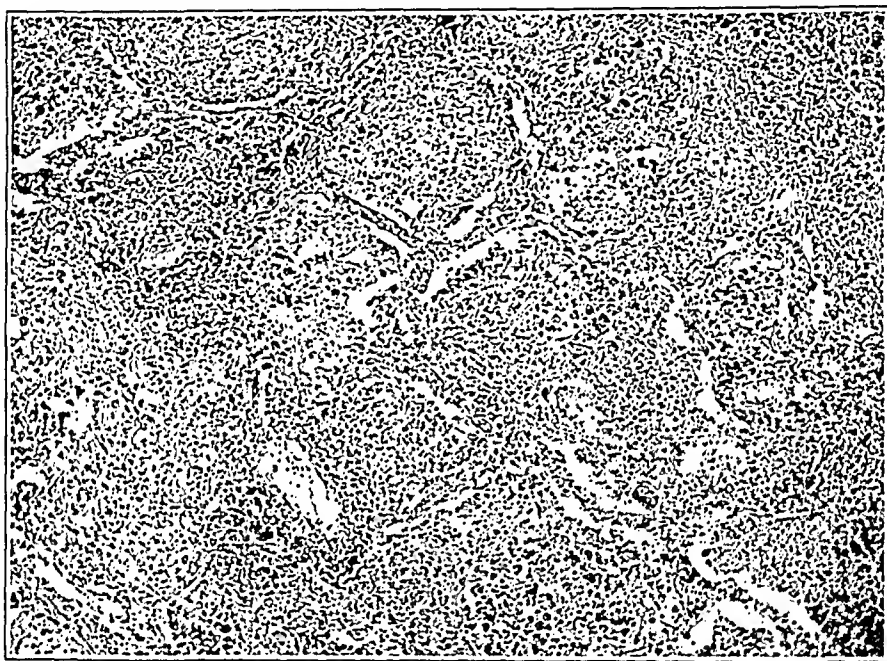


Fig 6 (case 2).—Photomicrograph of a lung, showing extensive pneumonia with destruction of the alveolar walls.

instance in which one was identified, tended to form coalescent caseous areas with beginning abscess production.

SUMMARY

Three cases of tularemia, two of which were diagnosed clinically and a third, pathologically, are reported.

The clinical course was characterized by sustained fever, tachycardia, dyspnea, prostration, delirium, signs of intoxication, extreme cyanosis, constipation and abdominal distention. In all three instances there was clinical evidence of pulmonary involvement.

At autopsy in each case, caseous nodules, usually small but sometimes in coalescent groups forming larger necrotic areas, were found in lymph nodes, the lungs, liver and spleen.

ACUTE, SUBACUTE AND CHRONIC ISOLATED MYOCARDITIS

REPORT OF A CASE

MORRIS A. SIMON, M.D.

AND

SIDNEY WOLPAW, M.D.

CLEVELAND

Acute isolated myocarditis is a rare form of heart disease, first clearly described by Fiedler in 1889. In the American literature attention was first called to this entity in 1929 by Scott and Saphir¹ in their report of two cases. The latter paper contains bibliographic references to the thirty-six cases previously recorded. Search of the literature since 1929 reveals reports of at least ten other cases in which the histologic pictures correspond to that of acute isolated myocarditis (one each by Gallavardin and Gravier,² Legrand and Nayrac,³ Mazzeo,⁴ De La Chapelle and Graef,⁵ Bailey and Andersen,⁶ Boikan,⁷ Bessem and Elsbach,⁸ Maxwell and Barrett,⁹ Miller¹⁰ and Maslow and Lederer¹¹). Boikan's case is described under the title "Myocarditis Perniciosa";

From the Departments of Pathology and Medicine of the City Hospital.

1. Scott, R. W., and Saphir, O.: Acute Isolated Myocarditis, *Am. Heart J.* **5**:129 (Dec.) 1929.

2. Gallavardin, L., and Gravier, L.: Subacute Myocarditis with Interstitial Lesion; *Case, Arch. d. mal. du coeur* **22**:379 (June) 1929.

3. Legrand, R., and Nayrac, P.: Primary Interstitial Myocarditis of Anemic Origin, *Compt. rend. Soc. de biol.* **100**:886 (April 8) 1929.

4. Mazzeo, A.: Interstitial Myocarditis in a Child Two Years Old, *Pediatrics* **37**:768 (July 15) 1929.

5. De La Chapelle, C. E., and Graef, I.: Acute Isolated Myocarditis with Report of a Case, *Arch. Int. Med.* **47**:942 (June) 1931.

6. Bailey, F. R., and Andersen, D. H.: Acute Interstitial Myocarditis, *Am. Heart J.* **6**:338 (Feb.) 1931.

7. Boikan, W. S.: Myocarditis Perniciosa, *Virchows Arch. f. path. Anat.* **282**:46, 1931.

8. Bessem, N., and Elsbach, E. M.: Isolated Acute Interstitial Myocarditis as Cause of Sudden Death, *Geneesk. tijdschr. v. Nederl.-Indië* **71**:1045 (Sept. 15) 1931.

9. Maxwell, E. S., and Barrett, C. C.: Acute Interstitial Myocarditis: Report of Case Following Severe Dermatitis Due to Sulphur Ointment, *Arch. Dermat. & Syph.* **29**:382 (March) 1934.

10. Miller, J.: Granulomatous Myocarditis, *Canad. M. A. J.* **29**:134 (Aug.) 1933.

11. Maslow, H. L., and Lederer, M.: Interstitial Myocarditis in Child Nineteen Months of Age, *Am. J. Dis. Child.* **45**:807 (April) 1933.

Miller's under the term "Granulomatous Myocarditis." An exact distinction between the advanced stages of myocarditis thus described and the various grades of change which may be noted in the myocardium in individual cases of isolated myocarditis is not possible with present knowledge.

Acute isolated myocarditis is characterized by a distinctive histologic picture. The myocardium shows a diffuse infiltration of the interstitial tissues by lymphocytes, mononuclear cells and, to a lesser degree, polymorphonuclear leukocytes, eosinophils and plasma cells. Numerous fibroblasts and new blood vessels may be seen. Occasionally small areas of necrosis are found in the muscle fibers themselves, but these are usually spared. The same heart may show a picture varying from that of cellular infiltration to those of the various stages of fibrosis. The endocardium and pericardium are usually not involved in the process, the lesion being entirely confined to the myocardium. The remainder of the body likewise shows no changes corresponding to the myocardial lesion, passive hyperemia and infarcts secondary to mural thrombi being the common findings.

Clinically, no distinctive picture exists by which the lesion may be diagnosed with any degree of assurance. Instances of sudden death without the previous occurrence of cardiac symptoms have been reported, as in Legrand and Nayrac's³ 69 year old patient who died of rupture of the left ventricle four days after apparent recovery from a convulsive seizure. In a small number of cases the duration of illness extended from nine to twenty-one months, the picture in prolonged disease being one of severe congestive failure with all of the classic signs and symptoms. The usual course, however, is one of rapid and progressive myocardial insufficiency, the total illness frequently being measured in terms of weeks, with dyspnea, cyanosis, tachycardia and weakness as the outstanding symptoms. Thus, in the case of De La Chapelle and Graef,⁵ only five weeks elapsed between the onset of cardiac symptoms (cough, shortness of breath, bloody sputum, edema) and death.

The condition has been described in both males and females; in the young and in the old. Of the recent cases Mazzeo's⁴ was in a child aged 2 years; Maslow and Lederer's¹¹ in an infant of 18 months. The greatest number of cases appears between the ages of 20 and 50.

Examination of the heart itself usually yields negative results. The cardiac sounds have been described as being muffled, and occasional apical systolic murmurs have been heard. The significant physical findings are usually those of myocardial failure. The few electrocardiographic studies thus far recorded have been of little assistance in formulating a specific clinical diagnosis. Thus the electrocardiograms in the two cases of Scott and Saphir showed only left ventricular pre-

ponderance; that of De La Chapelle and Graef showed a prolonged PR interval, complete intraventricular block and low voltage in all leads with a normal sinus rhythm.

Accurate clinical diagnosis has also been rendered more difficult by the obscurity of the etiologic factors. Infection has most frequently been called the causal agent. In a few cases a history of rheumatic fever has been obtained. In others more or less remote infections (burns, gonorrhea, influenza, measles) have occurred, but a direct relationship between such infections and acute isolated myocarditis has not been established by either bacteriologic or histologic studies. In many cases neither a history of infection nor clinical evidence of its presence has been found.

REPORT OF A CASE

History.—J. M., a 23 year old white man, was first seen in the medical outpatient department of the City Hospital on March 20, 1934. The patient considered himself perfectly well until four weeks previously, when he noted shortness of breath and slight edema of the lower extremities. Prior to this time, according to the patient, he had been able to do hard manual labor. There was no history of acute rheumatic fever or of growing pains. No history of an infection could be obtained. Six months before, the patient had a severe rhinitis, from which he had recovered without complication. He said that he had not had gonorrhea or syphilis. There was no history of contact with tuberculosis.

Examinations.—The patient revealed cyanosis of the face and neck, distention of the jugular veins and a few râles at the bases of the lungs. He was moderately short of breath. There was increased precordial activity, the apex being in the sixth intercostal space in the anterior axillary line. The heart sounds were distant; there were no murmurs. A tender liver was palpable 1 fingerbreadth below the right costal margin. There was slight peripheral edema. The temperature was 37 C. (98.6 F.); the pulse rate was 112; the blood pressure was 110 systolic and 75 diastolic. Digitalis and rest in bed afforded no relief.

The patient was again seen in the clinic on March 27, presenting the same picture. Fluoroscopic examination and an x-ray film of the heart showed an enlargement of the cardiac shadow mainly in the left ventricular region. The aortic knob was effaced, and there was bulging in the region of the pulmonary artery and left auricle. The right side of the diaphragm was slightly elevated. The pulmonary fields were clear. There was no pathologic process in the mediastinum. The patient finally consented to enter the hospital on the evening of March 31.

On admission dyspnea and cyanosis were marked, and the patient was most uncomfortable. Examination of the eyegrounds showed them to be entirely normal. There was moderate jugular distention. Both lungs were filled with numerous coarse râles. The liver could be palpated 2 fingerbreadths below the right costal margin and was tender. There was slight pitting edema of the feet and ankles. The peripheral vessels were not sclerotic. There was no pulsus paradoxus. The femoral vessels were palpable.

Examination of the heart revealed findings similar to those already noted. The sounds appeared distant, and there was a short, soft, systolic murmur at the apex. The blood pressure was 90 systolic and 70 diastolic. The blood showed 5,150,000 red and 35,200 white cells per cubic millimeter, and 90 per cent hemo-

globin (Sahli). The Wassermann reaction of the blood was negative. The urea nitrogen was 49.1 mg., creatinine 3.8 mg., and sugar 64.3 mg., per hundred cubic centimeters. The urine contained albumin (2 plus). Sugar was not present. There were many hyaline and granular casts, many white blood cells and occasionally red blood cells.

Course.—The patient showed considerable improvement following venesection, intranasal administration of oxygen, and use of morphine and atropine in small doses. He was fairly comfortable during the night and the next morning, although no significant change in the physical signs was evident. Death occurred rather



Fig. 1.—A tangential section through the wall of the left ventricle to show the extent of myocardial damage. The upper arrow points to the type of lesion in the myocardium. The lower arrow points to a mural thrombus in the wall of the left ventricle.

suddenly about twenty hours after admission to the hospital and five and a half weeks after the onset of illness. The temperature was 37 C. (98.6 F.) until shortly before death, when it rose to 38.2 C. (100.7 F.). The pulse rate varied between 80 and 100 and the respirations between 24 and 30. No electrocardiogram was obtained. The clinical diagnosis submitted was: cardiac hypertrophy and dilatation, with myocardial insufficiency—etiology undetermined.

Autopsy.—The body was well developed and exceedingly well nourished. It measured 180 cm. in length and weighed approximately 91 Kg. There was con-

siderable cyanosis of the face and neck. The peritoneal cavity contained 200 cc. of clear straw-colored fluid, the right pleural cavity 1,000 cc., the left pleural cavity 200 cc. and the pericardial sac 170 cc. On the posterior aspect of the right auricle a few fine fibrinous strands were seen on the epicardium. The heart as seen in situ was a peculiar yellowish pink and exceedingly flabby.

The heart weighed 450 Gm. The shape was somewhat distorted by the fact that all the chambers were dilated and filled with fresh blood clot and the heart flabby. The epicardial surface was everywhere thin, smooth and glistening, except on the posterior aspect where small irregular depressed areas were present, over which a small amount of fibrin was seen. When the heart was viewed externally, a number of oblong depressed purple soft areas on the anterior and posterior surfaces of the heart were present. The interior of the auricles was not remark-

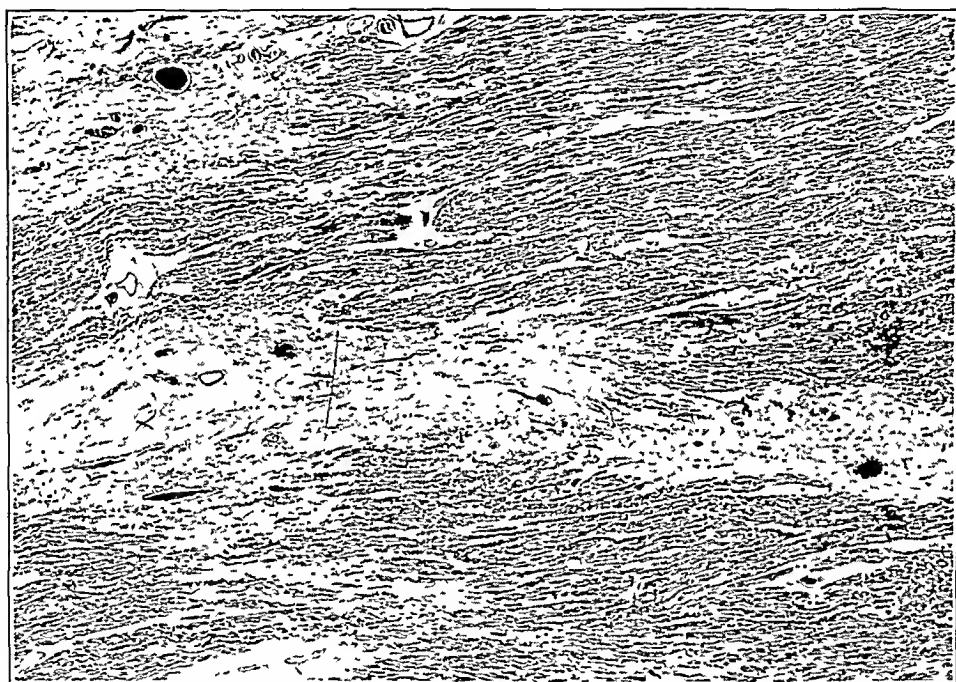


Fig. 2.—Relatively old areas of fibrous connective tissue in the myocardium. Hematoxylin and eosin; $\times 25$.

able. All the valve leaflets were thin, smooth and pliable and showed no gross pathologic changes. Both ventricles showed distinct flattening of the columnae carnae; their chambers were slightly enlarged, and through the endocardium could be seen depressed oblong violaceous areas similar to those seen on the outer surface.

Many sections through the myocardium revealed a peculiar mottled pinkish-yellow discoloration. Section through the violaceous areas showed that they were poorly demarcated and of distinctly gelatinous appearance. In the apex of both the right and the left ventricle an organizing mural thrombus was found densely adherent to the myocardium and enmeshed in the interstices of the columnae carnae. The coronary arteries were carefully explored and revealed the usual caliber with thin smooth intimal surfaces without thrombus or embolus.

The lungs showed edema and passive hyperemia. No infarcts were present.

The kidneys and the spleen showed passive hyperemia and recent infarcts. A few of the veins about the prostate showed thrombosis, but careful search through all the organs failed to reveal any focus of suppuration or infection. The rest of the veins showed only passive hyperemia. The postmortem culture of blood from the heart was sterile; the autopsy had been performed fourteen and one-half hours after death. Permission for removal of the brain was not obtained.

Microscopic Examination.—Many sections of the myocardium showed inflammation, variable as to degree and character. The inflammation was essentially interstitial and diffuse, although focal areas of inflammation were not infrequently present. In the diffuse areas of inflammation there was an abundant infiltration by plasma cells, lymphocytes and polymorphonuclear leukocytes, and many of the latter type were eosinophils. In some places the inflammatory change was more

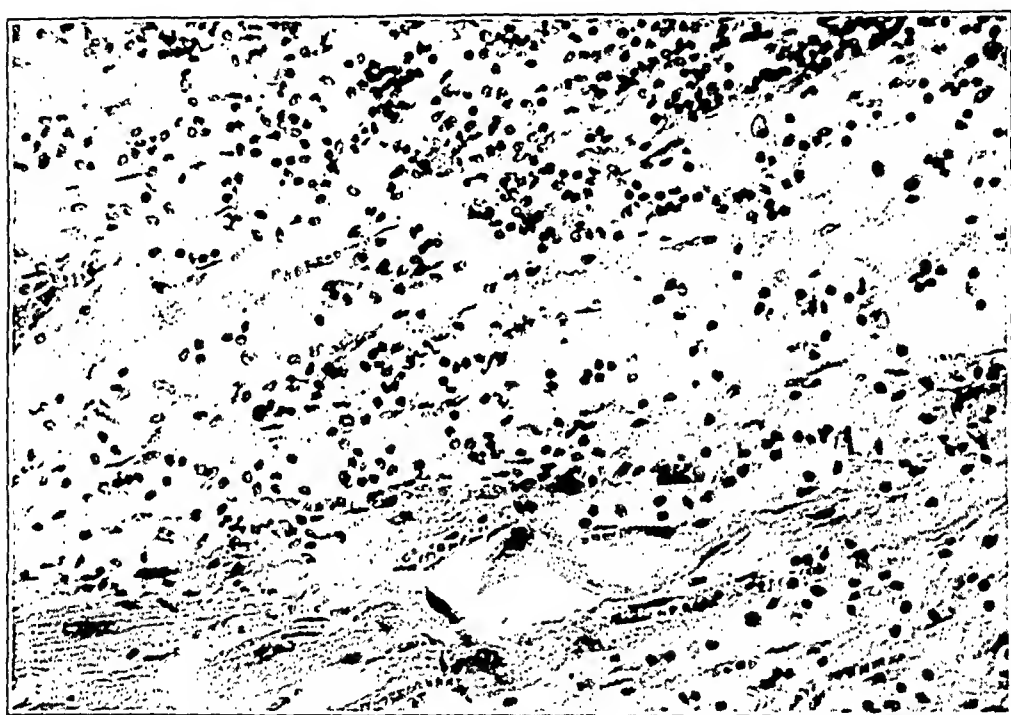


Fig. 3.—An area of acute and subacute inflammation with destruction of myocardial fibers and disorganization of architecture.

acute and the polymorphonuclear leukocytes were more numerous, whereas in other situations acellular fibrous scars replacing muscle fibers were not infrequent. In some areas there was actual granulation tissue present with new capillary formation and fibroblastic proliferation. The majority of the lesions were found in perivascular situations, although many were isolated in the myocardium remote from vessels. The inflammatory reaction invaded and destroyed the myocardial fibers, and many showed a granular type of necrosis. Extensive necrosis was absent, and no giant cells were present. The epicardium overlying areas of acute inflammation showed a deposition of fibrin on the outer surface. In none of the sections studied did the appearance of the exudate suggest rheumatic fever. Nothing that can be interpreted as Aschoff bodies was seen. The vessels were not remarkable. Sections stained by the Ziehl-Neelsen and Gram methods failed to reveal the presence of organisms.

COMMENT

The clinical picture in this case was unusual because of the progressive and rapid myocardial failure in a young man without apparent cause. The patient's age made the diagnosis of coronary sclerosis doubtful. Neither the history nor the physical findings indicated a congenital cardiac lesion or an organic valvular lesion. Acute pericarditis and pericardial effusion could not be substantiated from physical signs and the previous fluoroscopic examination. The lack of any evidence in the history or clinical examination of acute infection antedating the present illness tended to rule out the usual picture of acute myocarditis secondary to infection. The most likely possibility appeared to be some unusual form of rheumatic myocarditis. However, the lack of a history of rheumatic infection, the inability to demonstrate pericardial involvement or a valvular lesion, the absence of fever, the ability of the patient to be up and around until his admission to the hospital rendered it unlikely that rheumatic fever was the cause. The clinical diagnosis submitted recognized the impossibility of ascribing, with any degree of certainty, a causative agent to explain a cardiac lesion so severe that but five and one-half weeks elapsed between apparent health and death.

Because it is a rare disease and because pathognomonic signs of its presence are yet to be described, the clinical recognition of acute isolated myocarditis rests, perhaps, on diagnosis by exclusion. In some cases the history only is characteristic. Therefore, in any young person with a history of rapid and progressive myocardial failure the exclusion of the ordinary etiologic factors, especially rheumatic fever, should always lead to the consideration of acute isolated myocarditis as the clinical diagnosis.

The extent of damage to the myocardium is both grossly and microscopically severe and explains perhaps the short duration. Old fibrous scars are present which must have antedated the onset of symptoms. These scars are probably inflammatory in origin, since vascular changes are not present. The apparent difference in the age of the changes suggests that, whatever the etiologic agent, it had been operating for a considerable period of time—until the functional mass of muscle was reduced below the level necessary for life. It is probable that this inflammatory process was present and subclinical in its manifestations for some time before the patient died. There is nothing in the microscopic appearance of the myocardial lesions to suggest a specific granuloma. Careful search also failed to reveal the changes associated with rheumatic myocarditis, in the myocardium, endocardium, valves or vessels. The thrombosis seen in the periprostatic venous plexus was secondary to the failing circulation and showed no gross or microscopic evidence of infection.

CANCER AS A PROBLEM IN METABOLISM

HOWARD H. BEARD, PH.D.

NEW ORLEANS

Cancer has taken an enormous toll of human lives for the last three thousand years. It is only within the last thirty-five years that this disease has been studied from the experimental point of view. Woglom,¹ in the annual Gross lecture of the Philadelphia Pathologic Society in 1931, divided the latter period into three decades. In the first decade the limits within which malignant tumors can be transplanted were determined; a method of protecting against their inoculation was found; the resistance of the cancer cell to various agents was compared; its cultivation in vitro was begun; the hereditary nature of cancer in mice was predicated, and a transmissible sarcoma of the fowl was discovered. In the second decade the rate of growth of the cancer cell was determined, and two methods of producing tumors experimentally were discovered. In the third decade another method of inciting the growth of tumors was reported; the chemical nature of the carcinogenic hydrocarbons in tar was established; the amount of irritation necessary to initiate neoplasia was determined, and the age at which cancer is most frequent was established.

In the present, fourth, decade, even though it has not yet passed, much experimental work has been done on the metabolism of the cancer cell and on endocrine imbalance as a cause of tumors. I wish to outline some of this newer work. No attempt will be made to review all the published experimental evidence, but enough will be given to show that these newer points of view are proving to be of unusual importance to the understanding of the nature of the malignant process.

CARBOHYDRATE METABOLISM OF TUMORS

Warburg² and his co-workers began their first experiments on the metabolism of tumors in 1924. Since then similar studies have been

From the Department of Biochemistry, Louisiana State University Medical Center.

Read, in summary, before the Faculty Club of the Medical Center, Dec. 11, 1934, and before the members of the Eclat Club on their visit to New Orleans, Dec. 14, 1934.

1. Woglom, W. H.: Experimental Cancer Research, *Am. J. M. Sc.* **181**:157, 1931.

2. Warburg, O.: *The Metabolism of Tumors*, translated by Frank Dickens, New York, R. R. Smith, Inc., 1931.

carried out in many parts of the world. Figure 1 shows the Warburg manometric apparatus.

The tissues the respiration of which is to be determined are placed in the outer portion of the respiration bottle in a respiration medium of isotonic saline, Locke's or Ringer's solution. Potassium hydroxide is placed in the central compartment. The system is then washed out with oxygen, the stoppers and stop-cocks are closed, and the bottle is placed in a bath maintained constantly at 37 C. and is shaken

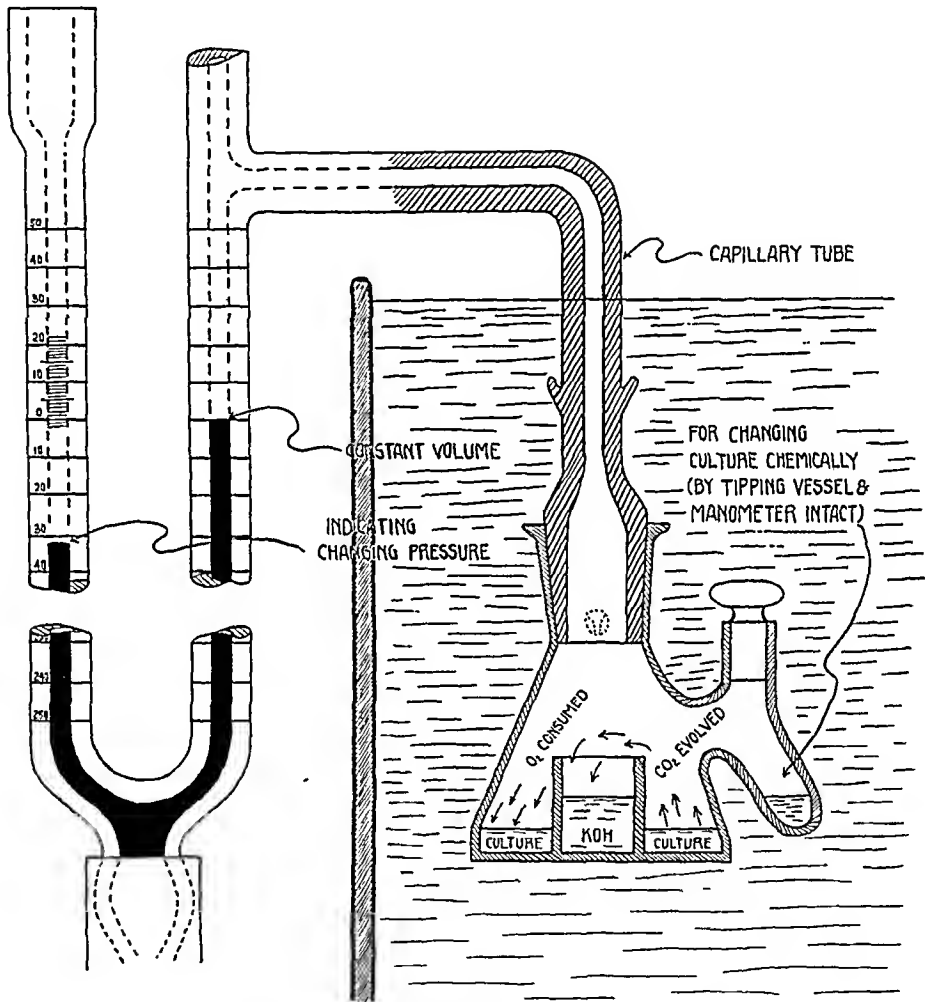
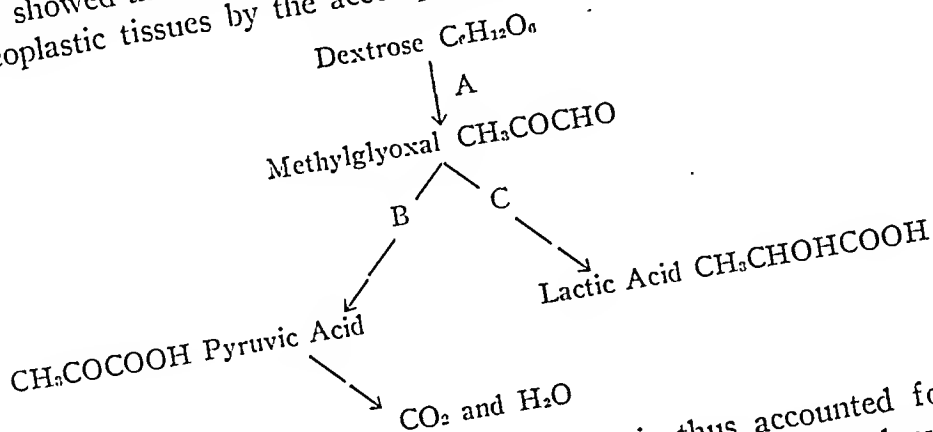


Fig. 1.—The Warburg manometric apparatus.

for stated lengths of time. As tissue respiration occurs, oxygen is consumed and carbon dioxide is evolved, which is absorbed by the alkali in the central compartment. The lowering of the pressure through the consumption of oxygen is measured on the manometer, which makes possible an accurate calculation of the oxygen consumed by the tissue.

Warburg showed that in tumor tissue in the absence of oxygen from ten to twenty times as much lactic acid is formed as in normal tissue. This excess glycolysis is not absolutely specific for tumor

tissue, since it is also found in brain and retina. Nevertheless, it is certain that the disturbance in tumor cells consists in their incapability of increasing oxidation in the same degree as glycolysis. Dickens and Simer³ showed the difference in the carbohydrate metabolism of normal and neoplastic tissues by the accompanying scheme.



The deficient oxidation of tumor tissue is thus accounted for by a break in the oxidative route B between methylglyoxal and pyruvic acid with an increased glycolysis along route C. As Warburg expressed it, "Interference with the respiration of a growing cell is, from the standpoint of the physiology of metabolism, the cause of tumors. If the respiration of a growing cell is disturbed, as a rule the cell dies. If it does not die a tumor cell results. This is no theory, but a comprehensive summary of all the measurements at present available."

Warburg's work has been confirmed by a number of investigators: Dickens,⁴ Dodds,⁵ Glover,⁶ Fischer-Wasels⁷ and others. Working with benign and malignant tumors of man, Glover found an exact correlation between the histologic malignancy and the anaerobic glycolysis. Boyland⁸ recently reviewed the work on the biochemistry of malignant tissue, and Dodds⁹ and Dickens,⁴ that on the carbohydrate metabolism.

3. Dickens, F., and Simer, F.: A Note on the Metabolism of Tumors, *Lancet* 2:10, 1930.

4. Dickens, F.: Cancer as a Problem in Tissue Metabolism, *Cancer Rev.* 6: 57, 1931.

5. Dodds, E. C.: Recent Biochemical Research with Special Reference to the Normal and Malignant Cell, *Am. J. Cancer* 15:2765, 1931.

6. Glover, E. C.: The Metabolism of Human Tumors, *Am. J. Cancer* 15: 1043, 1931.

7. Fischer-Wasels, B.: General Predisposition to Tumor Formation, *Wien. klin. Wchnschr.* 44:629, 1931.

8. Boyland, E.: The Biochemistry of Malignant Tissue, *Ann. Rev. Biochemistry* 3:400, 1934.

9. Dodds,⁵ p. 2765.

10. Footnote deleted by the author.

LIPOID METABOLISM AND CHOLESTEROL; IRRADIATION AND
CARCINOMA OF THE SKIN

Numerous workers have shown that there is an increase in both cell lipids and cell cholesterol in benign and malignant tumors (Yasuda and Bloor,¹¹ Roffo,¹² Roffo and Thomas,¹³ Burgheim and Joel,¹⁴ Marqués,¹⁵ Kirgreen,¹⁶ Willheim and Fuchs,¹⁷ Uramoto,¹⁸ Brikker and Lasaris,¹⁹ LeMay,²⁰ Jowett,²¹ Schaaf and Werner²² Tesauro²³ and others). Roffo,¹³ in his monograph, "La chimie du cancer," summarized the metabolic aspects of the cancer cell, together with the rôles played by lecithin, cholesterol and lipoids. It seems reasonable to believe that the cancer cell may utilize fat as a source of energy for its rapid growth. These studies of the cholesterol content of tumors are of much importance in cases of cancer of the skin.

Further work by Roffo²⁴ is interesting in this connection. He stated that the skin is more frequently attacked by cancer than any other

11. Yasuda, M., and Bloor, W. R.: Lipin Content of Tumors, *J. Clin. Investigation* **11**:677, 1932.

12. Roffo, A. H.: Heliotropism of Cholesterol in Relation to Skin Cancer, *Am. J. Cancer* **17**:42, 1933.

13. Roffo, A. H., and Thomas, J.: *La chimie du cancer*, Paris, Vigot Frères, 1933, pp. 110 and 120.

14. Burgheim, F., and Joel, W.: On the Relation Between Cancer and Lipoid Metabolism, *Klin. Wchnschr.* **10**:397, 1931.

15. Marqués, E. J.: The Action of Radiations on Cholesterol, *Néoplasmes* **12**:159, 1933.

16. Kirgreen, O.: Cholesterol Metabolism in Cancer Patients, *Arch. f. klin. Chir.* **177**:383, 1933.

17. Willheim, R., and Fuchs, G.: The Cholesterol Content of the Cancer Lipoids, *Biochem. Ztschr.* **247**:297, 1932.

18. Uramoto, M.: Studies on the Changes in the Amount of Cholesterol and Phosphorous Compounds of Cancerous Tissue at the Various Periods of Its Growth, *J. Biochem. (Japan)* **16**:69, 1932.

19. Brikker, F., and Lasaris, J.: The Lipoid Content of Cancer Tissue, *Ztschr. f. Krebsforsch.* **37**:432, 1932.

20. LeMay, P.: Lipoids and Cancer, *Néoplasmes* **10**:158, 1931.

21. Jowett, M.: The Phosphatide and Cholesterol Content of Normal and Malignant Human Tissues, *Biochem. J.* **25**:1991, 1931.

22. Schaaf, F., and Werner, A. J.: The Relation of Cholesterol, Phosphatide and Total Fat Content of the Blood to the Origin of Xanthoma, *Arch. f. Dermat. u. Syph.* **162**:217, 1930.

23. Tesauro, G.: The Influence of Lipids upon Tumor Growth, *Ztschr. f. Krebsforsch.* **35**:269, 1932.

24. (a) Roffo, A. H.: Cancer y sol: El desarrollo experimental de tumores espontaneos por las irradiaciones ultravioletas en relacion con el heliotropismo de la colessterina, *Bol. Inst. de med. exper. para el estud. y trat. del cáncer* **10**:417, 1933. (b) Roffo.¹²

organ of the body. Table 1 gives the incidence of carcinoma in different parts of the face in 2,000 patients examined at the Buenos Aires Cancer Institute. About the same frequencies were observed by Nielsen²⁵ in 1,000 patients with skin cancer in the Radium Station in Copenhagen. In the Negro, in whom pigmentation of the skin prevents absorption of light, carcinoma of the skin, according to Roffo, is rare.²⁶ He showed that rat and human tumors may contain more than twice the normal concentration of cholesterol (fig. 2), and that it is possible, by keeping animals on a cholesterol-free diet, to modify the soil in such a way as to inhibit or prevent the growth of tumors. He expressed the belief that exogenous dietary factors and pregnancy are also responsible for the increased cholesterol content of the blood and precancerous growths. The large amount of cholesterol in the skin of the face is due, according to Roffo, to the exposure of the face to sunlight. The cholesterol concentration in the skin of the face is two or three times that in the skin of the abdomen, which is usually protected from the sun by clothing.

TABLE 1.—Cancer of the Face

	Per Cent
Nose.....	61.4
Cheek.....	18.0
Ear.....	7.9
Forehead.....	7.7
Temporal region.....	4.0

Roffo²⁷ showed that while ultraviolet rays of wavelengths from 3,900 to 2,300 angstroms exerted no inhibition on the growth of the fibroblasts of chicken heart or rat sarcoma, the luminous rays of wave-

25. Nielsen, J.: Cancer of the Skin, Ugesk. f. læger **95:464**, 1933.

26. Dr. J. K. Howles, in a recent survey of 1,987 cases of epithelioma of the skin observed at Charity Hospital in New Orleans over a period of twenty-seven years, gave its incidence among the white and colored races as follows:

Site	Cases	Racial Distribution	
		White	Colored
Cheek.....	616	593	18
Lips.....	458	463	20
Nose.....	360	354	6
Ears.....	126	123	3
Neck.....	91	89	2
Forehead.....	125	124	1
Eyes.....	88	85	3
Chin.....	44	41	3
Mouth.....	49	41	8

27. Roffo, A. H.: Comparison of Luminous and Ultraviolet Rays on Growth of Normal and Neoplastic Cells in Tissue Culture, Bol. Inst. de med. exper. para el estud. y trat. del cáncer **10:209**, 1933.

lengths from 7,000 to 3,900 angstroms inhibited the growth of the fibroblasts of chicken heart in four hours and of those of sarcoma in two hours.

Correa²⁸ summed up Roffo's views on the relationship of cholesterol to cancer as follows:

Cholesterol seems to be the substance which acts in preponderant form: Though it has not yet been possible to establish exactly the relation of cause to effect, the evidence accumulated by Professor Roffo seems to ascribe to cholesterol a positive position in the preparation of the soil and consequently in the genesis and evolution of malignant tumors. This evidence is as follows:

1. The cholesterol increase in neoplastic tissue, blood and cholesterologenous organs



Fig. 2.—A precancerous lesion of the face. The cholesterol content of tissue from the area indicated was 1.1 Gm. per hundred grams of tissue; that of normal skin is 0.49 Gm. per hundred grams of tissue. (Courtesy of Prof. A. H. Roffo.)

2. The absorption of cholesterol by malignant tumors, shown in vivo and in vitro
3. The cholesterol contents according to age, and the relation between the maximum content and the frequency of tumors
4. Its presence in precancerous stages
5. The photo-active function and the deposits of cholesterol in parts of the skin exposed to the sun
6. The localization of skin tumors in these parts

28. Correa, L. M.: Los lípidos en el cáncer: Investigaciones efectuadas en el Instituto de Medicina Experimental, Bol. Inst. de med. exper. para el estud. y trat. del cáncer 10:511, 1933.

Roffo ^{24a} recently subjected rats to ultraviolet radiation, beginning with a daily five minute exposure, which was gradually increased to one of twenty hours. The latter was given daily for from six to eight months. Tumors on the eyes, ears and back of the head were produced (fig. 3). Herlitz, Jundell and Wahlgren,²⁹ Findlay³⁰ and Putschar and Holtz³¹ also produced malignant growths in rats and other animals by irradiation. These observations are being confirmed by me.

Mandel³² showed that irradiation of the ovaries of rats from 7 to 10 days of age was followed by precocious opening of the vagina and estral changes at approximately 22 days of age. The irradiated ovaries at this time revealed huge follicles with enormous antrums. The roentgen treatment greatly stimulated the growth of the follicles, which then became functionally hyperactive. These results, together with

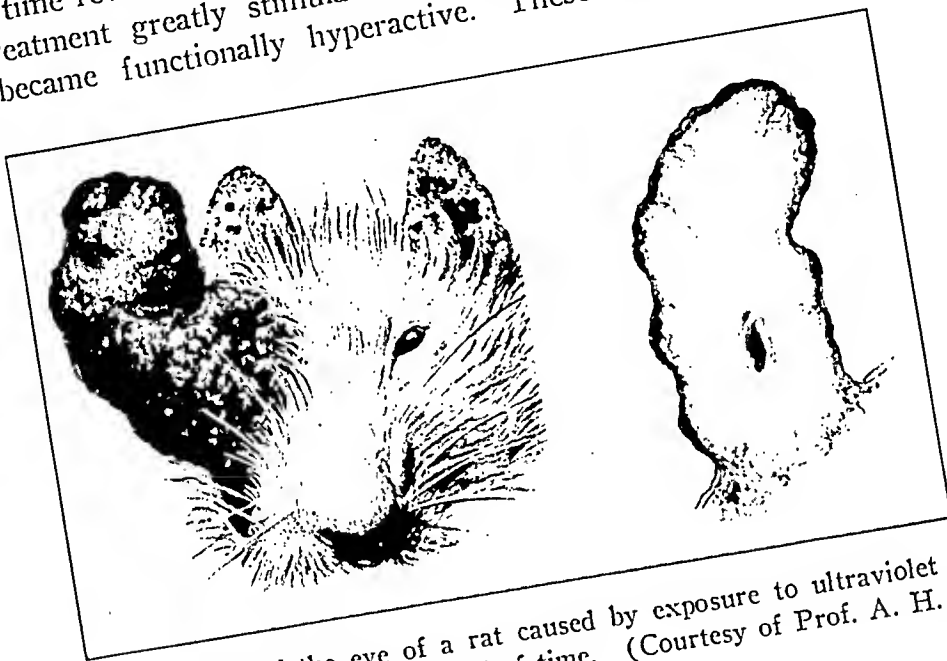


Fig. 3.—Tumor of the eye of a rat caused by exposure to ultraviolet rays in increasing amounts over a long period of time. (Courtesy of Prof. A. H. Roffo.)

those mentioned in the foregoing paragraph, show that prolonged irradiation may produce cancerous changes while moderate doses may cause estral changes. Dodds³³ showed that either irradiation or vitamin D can produce estral changes.

29. Herlitz, C. W.; Jundell, I., and Wahlgren, F.: Weitere Untersuchungen über die Wirkung einiger Sterine und des ultravioletten Lichtes auf weisse Mäuse, *Acta pædiat.* **12**:221, 1932.

30. Findlay, G. M.: Cutaneous Papillomata in the Rat Following Exposure to Ultraviolet Light, *Lancet* **1**:1229, 1930.

31. Putschar, W., and Holtz, E.: The Production of Carcinoma of the Skin in Rats by Long Continued Ultraviolet Irradiation, *Ztschr. f. Krebsforsch.* **33**:219, 1931.

32. Mandel, J.: Ovarian Irradiation and Sexual Precocity in the Rat, *Proc. Soc. Exper. Biol. & Med.* **32**:155, 1924.

33. Dodds, E. C.: The Hormones and Their Chemical Relations, *Lancet* **1**:987, 1934.

Sumi and Nakahara³⁴ found that the absorption bands of 10 per cent aqueous extracts of four types of tumors (Rous chicken sarcoma, Fujinawa rat sarcoma, Flexner-Jobling rat carcinoma and Bashford mouse carcinoma), measured with the Hilger quartz spectrograph, type E-6, extended from 3,000 to 2,500 angstrom units with the center at 2,700 angstrom units. The intensity of absorption seemed greater in rat carcinoma, but this and mouse carcinoma showed much stronger absorption than did chicken sarcoma.

Gurwitch³⁵ of Leningrad, addressing the International Congress on Cancer in Madrid in 1933, stated that malignant tissue, as well as any aggregation of proliferating cells, can give off ultraviolet radiations, which can then induce mitosis. This was shown as follows: A quartz spectrograph which had a scale of wavelengths instead of a photographic plate was placed between a tumor and a yeast culture. The tumor was placed in front of the slit of the spectrograph, and a series of yeast cultures was placed in front of the different divisions on the spectrographic scale. Stimulation occurred at some wavelengths but not at others. He stated that the emission of ultraviolet rays occurs as the result of many chemical reactions. Only the blood, nerves, muscles and small intestine were found capable of emitting the rays.

Matsuzki³⁶ recently showed that the intensity of ultraviolet absorption is greater in rat sarcoma than in rat carcinoma.

THE CARCINOGENIC HYDROCARBONS

Dodds,³³ in his second Goulstonian lecture, delivered before the Royal College of Physicians at London on March 8, 1934, discussed the recent work on the carcinogenic hydrocarbons and their relation to the female sex hormone, estrin.

Yamagiwa and Ichikawa³⁷ first showed, in 1915, that tar painting produced cancer in rabbits. This significant observation has stimulated an immense amount of work on the subject of tar cancers. Woglom³⁸ reviewed 290 papers on this subject published previous to the end of 1926, and Seelig and Cooper³⁹ listed 391 in 1933. The most recent work in this connection has been reported by Dodds.³³

34. Sumi, M., and Nakahara, W.: Ultraviolet Absorption Spectra of Tumor Extracts, Especially of Rous Chicken Sarcoma, *Gann* **26**:175, 1932.

35. Gurwitch: Foreign Letters, *J. A. M. A.* **102**:386 (Feb. 3) 1934.

36. Matsuzki, I.: Spectrographic Pathological Studies of Malignant Tumors, *Tr. Jap. Path. Soc.* **23**:719, 1933.

37. Yamagiwa and Ichikawa: *Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo* **15**:295, 1915; **17**:19, 1917; **19**:483, 1918.

38. Woglom, W. H.: Experimental Tar Cancer, *Arch. Path.* **2**:532 (Oct.) 1926.

39. Seelig, M. G., and Cooper, Z. K.: A Review of the Recent Literature of Tar Cancer, *Am. J. Cancer* **17**:589, 1933.

At first it was thought that the tar produced a chronic irritation which later prepared the tissue for a malignant change. But not all tars will produce cancer when painted on the skin. The observations of Kennaway,⁴⁰ of Cook, Hieger, Kennaway and Mayneord,^{41a} of Cook^{41b} and of Cook, Hewett and Hieger^{41c} in England are very important in this connection. Kennaway showed that by heating isoprene or acetylene in the presence of hydrogen a carcinogenic agent could be produced which contained only carbon and hydrogen. In 1927 Mayneord studied the spectra of such synthetic mixtures and observed their similarity to the spectrum of the carcinogenic tar. Hieger, also, had observed the resemblance between the fluorescence spectrum of benzantracene and a carcinogenic coal tar. Benzantracene, however, is only weakly carcinogenic.

Clar⁴² had previously synthesized di-benzanthracene, which gave 58 cancers and 9 papillomas in 190 mice, of which only 140 lived more than six months. Benzantracene consists of four benzene rings, while di-benzanthracene adds one more benzene ring in a certain position. Tumors have been produced in similar fashion in fowls by Burrows⁴³ and Peacock.⁴⁴ Lacassagne⁴⁵ injected a solution of 1, 2, 5, 6-di-benzanthracene into the testicle of a rabbit; at the site of the injection a malignant epithelial tumor appeared which produced numerous metastases in the lungs. Cook and co-workers⁴¹ then showed that a group of compounds chemically related to 1:2—benzantracene were carcinogenic when applied to animals.

Figure 4 shows the structural chemical relationship between the bile acids, the male and female sex hormones, cholesterol, ergosterol, calciferol (vitamin D) and the carcinogenic hydrocarbons. Somewhat

40. Kennaway, E. L.: The Formation of a Cancer Producing Substance from Isoprene, *J. Path. & Bact.* **27**:233, 1924; Experiments upon Cancer Producing Substances, *Brit. M. J.* **2**:1, 1925; Further Experiments upon Cancer Producing Substances, *Biochem. J.* **24**:497, 1930.

41. (a) Cook, J. W.; Hieger, I.; Kennaway, E. L., and Mayneord, W. V.: The Production of Cancer by Pure Hydrocarbons, *Proc. Roy. Soc., London*, s.B **111**:455, 1932. (b) Cook, J. W.: The Production of Cancer by Pure Hydrocarbons, *ibid.* **111**:485, 1932. (c) Cook, J. W.; Hewett, C. L., and Hieger, I.: Coal Tar Constituents and Cancer, *Nature* **130**:926, 1932.

42. Clar, E.: Zur Kenntnismehrernigen aromatischer Kohlenwasserstoffe und ihrer Abkömmlinge: I. Mitteilung Dibenzantracene und ihre Chinone, *Ber. d. deutsch. chem. Gesellsch.* **62** B:350, 1929.

43. Burrows, H.: A Spindle-Celled Tumor in a Fowl Following Injection of 1:2:5:6 Di-Benzanthracene in a Fatty Medium, *Am. J. Cancer* **17**:1, 1933.

44. Peacock, P. R.: Production of Tumors in Fowls by Carcinogenic Agents, *J. Path. & Bact.* **36**:141, 1933.

45. Lacassagne, A.: Essais de production de cancer chez le lapin au moyen du 1-2-5-6, dibenzanthracène, *Compt. rend. Soc. de biol.* **114**:660, 1933.

the same structure has also been given for the cardiac aglucones by Jacobs and Elderfield⁴⁶ and Tschesche.⁴⁷

The extensive researches of the English workers referred to have shown that these carcinogenic hydrocarbons may be formed from the naturally occurring bile acids⁴⁸ and sterols by the chemical reactions of reduction, dehydration and dehydrogenation. They might also arise from the degradation products of the sterols in the body.

According to Dodds, 1:2 benzpyrene will produce cancer in about half the time that is required by 1, 2, 5, 6-di-benzanthracene. This finding has been confirmed by Maisin and Liégois⁴⁹ and by Sonnie and Truhaut.⁵⁰ It is therefore the most active carcinogenic agent known. The phenanthrene ring type of compound has recently been shown to be a normal constituent of the body. By taking the absorption spectrum with a small quartz spectrograph, it will be possible to detect these carcinogenic agents in tar and oils and thus protect industrial employees against them.

Another line of investigation has shown that the compounds of the closely related phenanthrene group are capable of causing estrus in small castrated animals. Cook and Dodds⁵¹ observed full estrus

46. Jacobs, W. A., and Elderfield, R. C.: The Structure of the Cardiac Aglucones, *Science* **80**:533, 1934.

47. Tschesche, R.: *Angewandte Chem.* **47**:729, 1934.

48. Sellards (Ulceration of the Stomach and Necrosis of Salivary Glands Resulting from Experimental Injection of Bile Salts, *Arch. Int. Med.* **4**:502 [Nov.] 1909) and Tashiro and co-workers (*M. Bull. Univ. Cincinnati* **6**:110, 124, 130, 134 and 144, 1931) observed the development of gastric ulcers in guinea-pigs following intraperitoneal injection of bile salts. These important results have been confirmed by Anderson and Farmer (Development of Gastric Ulcers and Decrease in Reducing Power of Adrenals Following Injection of Bile Salts, *Proc. Soc. Exper. Biol. & Med.* **32**:31, 1934), who stated: "We injected approximately 40 guinea pigs with varying amounts of bile salts (Fairchild's). The expected individual variations in susceptibility were observed, but injections of 0.1 gm. or more generally caused death and extensive ulceration of the gastric mucosa. The latter was usually so marked that the site of the ulcers could be plainly observed from the outer surface of the stomach, appearing as thin, semi-transparent areas. In three animals perforation occurred, gastric contents being found in the peritoneal cavity at autopsy." In view of the fact that a gastric ulcer may later develop into gastric cancer, the foregoing findings are of interest at this time.

According to Science (*Science* [suppl.] **80**:14 [Dec. 28] 1934), Dr. Cook and associates at the London Free Cancer Hospital have recently transformed, by simple chemical means, a naturally occurring bile acid into a cancer-producing substance.

49. Maisin, J., and Liégois, P.: Carcinogenicity of Benzpyrene, *Compt. rend. Soc. de biol.* **115**:733, 1934.

50. Sonnie, C., and Truhaut, C.: Carcinogenic Chemicals, *Bull. Assoc. franç. p. l'étude du cancer* **23**:6, 1934.

51. Cook, J. W., and Dodds, E. C.: Sex Hormones and Cancer Producing Compounds, *Nature* **131**:205, 1933.

when 100 mg. of 1:2 benzpyrene or 5:6:cyclopenteno-1:2:benzanthracene was injected. However, these compounds are much more carcinogenic than estrogenic. According to Dodds, di-benzanthracene is carcinogenic in the aromatic state and estrogenic when suitably hydrogenated and supplied with hydroxyl groups.

ENDOCRINE IMBALANCE IN THE PATHOGENESIS OF SOME TYPES OF CANCER

Schoonover ⁵² in 1931 discussed the changing attitude toward cancer, stressing the importance of studies of cell physiology and cell chemistry

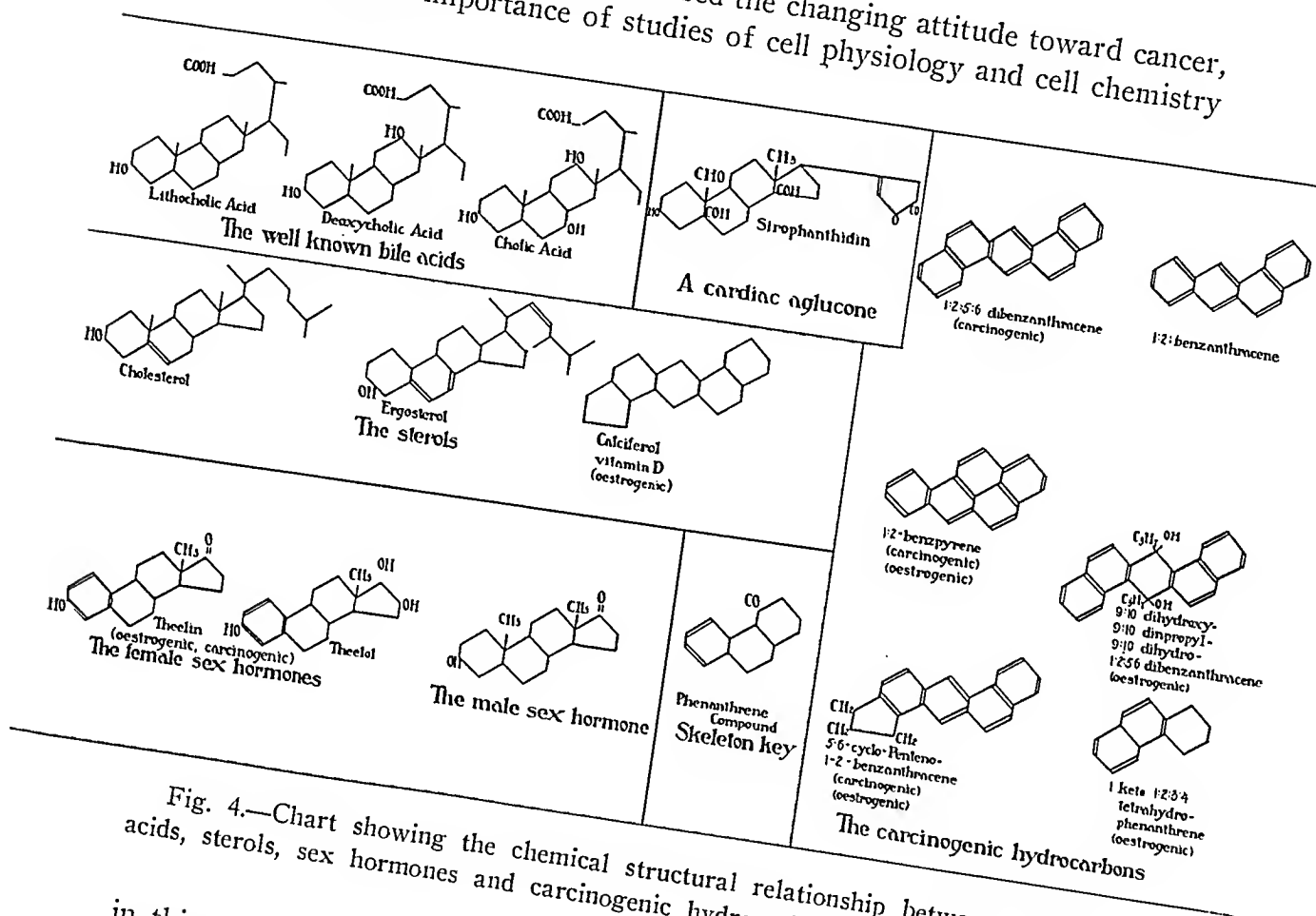


Fig. 4.—Chart showing the chemical structural relationship between the bile acids, sterols, sex hormones and carcinogenic hydrocarbons.

in this connection. He concluded that studies of cell physiology indicate that cancer is a phenomenon of normal cells which have grouped themselves into masses, typical of tumors, because of the presence of a chemical substance. This substance is present in tar, paraffin, soot, certain chemicals, the products of chronic inflammation and possibly certain foods. Endocrine imbalance as a cause of certain types of cancer has been suggested by a number of workers.

52. Schoonover, F.: The Changing Attitude Towards Cancer, Texas State M. J. 26:806, 1931.

The rapid growth of some tissues is evidently associated with the activity of the glands of internal secretion, especially with that of the thymus. The increase in size of the mammary glands at puberty and their enlargement during pregnancy, the growth of the antlers of the deer during the rutting season and the enormous growth of the reproductive organs of the salmon at the expense of their muscle tissue during the spawning season are cases in point.

Since Sugiura and Benedict⁵³ have published 137 references to work on the hormones in cancer, I shall list only the more important of them here. The very important advances that have recently been made in the isolation of different endocrine products and the discovery of their remarkable physiologic effects naturally lead one to speculate on the effect of these hormones in malignant conditions. For instance, Allen and Doisy⁵⁴ showed clearly that estrin is capable of producing the most extensive cell growth and proliferation of tissue. When injected into immature female animals it will, in the short space of two days, bring on the physiologic phenomenon known as estrus. These findings are of much importance in the understanding of the etiology of some types of carcinoma. I shall now discuss the evidence for estrin, prolan, extracts of testicle, spleen and thymus, insulin and extracts of adrenal cortex.

Estrin.—Burrows and Kennaway⁵⁵ observed some interesting results from the application of estrin to the nonepilated skin of the interscapular region in male and female mice. In the males the following changes were noted: (1) scrotal hernia; (2) atrophy of the testicles; (3) diminution in the size of the seminal vesicles; (4) enlargement of the posterior lobes of the prostate, and (5) obstruction to the outflow of urine, resulting in a greatly distended bladder, due to pressure from the enlarged prostate. In the females the following conditions were noted: (1) prolonged estrus; (2) accumulation of keratinized epithelium in the vagina, which caused obstruction and distention of the passage from the uterus; (3) great enlargement of the horns of the uterus, which resulted in the formation of palpable tumors during life; (4) pyometra and perimetritis, which were the causes of death, and (5) in some cases, vaginal accumulations that prevented the flow of urine, resulting in distention of the bladder and even hydronephrosis.

53. Sugiura, K., and Benedict, S. R.: The Influence of Hormones on the Growth of Carcinoma, Sarcoma and Melanoma in Animals, *Am. J. Cancer* **18**:583, 1933.

54. Allen, E., and Doisy, E. A.: An Ovarian Hormone: Preliminary Report on Its Localization, Extraction and Partial Purification in Test Animals, *J. A. M. A.* **81**:819 (Sept. 8) 1923.

55. Burrows, H., and Kennaway, N. M.: On Some Effects Produced by Applying Oestrin to the Skin of Mice, *Am. J. Cancer* **20**:48, 1934.

The brilliant investigations of the English workers on the carcinogenic hydrocarbons which I have commented on in foregoing paragraphs have an added significance at this time. Since it has been shown that the aforesaid anthracene compounds are capable of producing both cancer and estrus, it is of much importance to see whether the female sex hormones can also produce, or be associated with, benign and malignant tumors. These possibilities have been realized by several workers, as will be shown in the following paragraphs. It is fairly certain that the sex hormones in the body are derived from the sterols by a process that involves a partial loss of hydrogen atoms with the formation of four condensed rings, one being aromatic in character and one containing only five carbon atoms. Thus by dehydration of the sterols the sex hormones are formed. Reviewing these researches, Sir F. G. Hopkins stated:

It is difficult when faced with such relations not to wonder whether the metabolism of sterols, which when normal can produce a substance stimulating physiologic growth, may in very special circumstances be so perverted as to produce within living cells a substance stimulating pathologic growth.

Loeb,⁵⁶ as early as 1907, showed that it was possible to produce uterine tumors in various animals through the action of an internal secretion of the corpus luteum and mechanical factors. These formations were described as "deciduomata" and "placentomata" to indicate their tumor-like character and to emphasize the significance of such experiments for the analysis of tumor growth. Lathrop and Loeb⁵⁷ in 1916 observed that in strains of mice with a high incidence of spontaneous tumors those females that were ovariectomized before the age of 6 months showed a marked decrease in the incidence of tumors. Loeb⁵⁸ confirmed these findings in a later study. Lathrop and Loeb stated that

these results demonstrate experimentally for the first time the significance of an internal secretion, or hormone, for the development of cancer. It is very probable that mammary cancer is not an exception, and that other substances favoring growth are a factor in the development of carcinoma in other sites. In other tissues, long continued external irritation, and in still others a combination of both factors, may, perhaps, exert a similar effect. It seems probable that any factor which periodically or over long periods of time induces increments in growth energy may be a factor in the development of carcinoma.

56. Loeb, L.: Ueber die experimentelle Erzeugung von Knoten von Decidua-gewebe, *Centralbl. f. allg. Path. u. path. Anat.* **18**:563, 1907.

57. Lathrop, A. E. C., and Loeb, L.: Further Investigations on the Origin of Tumors in Mice: III. On the Part Played by Internal Secretion in the Spontaneous Development of Tumors, *J. Cancer Research* **1**:1, 1916.

58. Loeb, L.: Further Investigations on the Origin of Tumors in Mice, *J. M. Research* **40**:477, 1919.

Cori⁵⁹ showed that ovariectomy in cancerous strains of mice when they are about 3 weeks of age prevents mammary cancer from developing in them. Murray⁶⁰ showed that there is a time correlation between the appearance of mammary cancer in mice and their normal sex life. He⁶¹ was able to induce mammary cancers in castrated males with ovarian transplants, and in 1928⁶² showed, in a highly inbred strain of mice, that the presence of the ovary and of its secretions is of primary importance in the raising of the physiologic condition of the mice to the threshold of mammary carcinoma. These facts, according to Chidester,⁶³ show that gestation, lactation and parturition favor mammary cancer in tumorous stocks, and their absence prevents it.

Mazer⁶⁴ recently discussed the relation of some of the endocrine glands to abnormal mammary hyperplasias. The normal mammary gland depends on a pituitary-ovarian balance, and an imbalance here is believed by him to be the cause of these abnormalities of the breast. Susman⁶⁵ expressed somewhat the same view. He wrote:

That this activity of the anterior pituitary does not in itself cause cancer is evident from the fact that in 98 per cent. of healthy pregnant females the Zondek-Ashheim reaction is positive. The relationship of malignant disease with pregnancy, in that both types of cases may give a positive Zondek-Ashheim reaction, is interesting in two ways. In both there is a tumor present, but the obvious point of difference between the two is that in pregnancy the growth is controlled—a condition lacking in the malignant growth.

Susman also stated his belief that an imbalance between the anterior and the posterior lobe of the pituitary gland is an important factor in malignant growth. Two patients with advanced cancer were treated with solution of pituitary gland alone and 5 with solution of pituitary gland and theelin. One epithelioma began to separate and was enucleated after seven weeks of treatment. The growing edge disappeared within

59. Cori, C. F.: The Influence of Ovariectomy on the Spontaneous Occurrence of Mammary Carcinomas in Mice, *J. Exper. Med.* **45**:983, 1927.

60. Murray, W. S.: Some Effects of Ovariectomy upon Breeding Females, *Science* **75**:646, 1932.

61. Murray, W. S.: Factors Involved in Incidence of Spontaneous Mammary Cancer in Inbred Race of Mice, *Papers Michigan Acad. Sc., Arts & Lett.* **8**:411, 1928.

62. Murray, W. S.: Ovarian Secretion and Tumor Incidence, *J. Cancer Research* **12**:18, 1928.

63. Chidester, F. E.: Mammary Cancer and Elemental Imbalance, *Am. Med.* **40**:162, 1934.

64. Mazer, C.: The Endocrine Glands in Relation to Abnormal Breast Hyperplasias, with Particular Reference to Associated Nipple Bleeding and Its Treatment, *M. Rec.* **140**:417, 1934.

65. Susman, W.: The Rôle of the Pituitary in the Development of Cancer, *Brit. M. J.* **2**:794, 1931.

five days. All 7 patients showed regressive changes in the tumors, and their lives were definitely prolonged.

According to Hofbauer,⁶⁶ pregnancy in the human being is associated with hyperplastic and hypertrophic changes in the anterior lobe of the hypophysis as a response to chorionic stimuli. That radical changes occurring in association with the menopause induce certain structural alterations of the hypophysis is shown by many facts. The acquired constitutional predisposition of the multiparous woman to the development of cervical cancer during the early menopausal period is also, according to Hofbauer, due to an imbalance between pituitary and ovarian activity. He recently produced leukoplakia in the uterine cervix of the guinea-pig by repeated transplantations of bits of the anterior lobe of the pituitary gland.

Overholser and Allen⁶⁷ injected the genital hormones subcutaneously into ovariectomized monkeys. In all the animals epithelial hyperplasia occurred in the uterine cervix. In many regions, columnar epithelium was surrounded by stratified squamous epithelium. These lesions were diagnosed by Dr. James Ewing of New York City as typical of those of early cancer. Buzzi⁶⁸ stated that ovarian and uterine underdevelopment and dysfunction predispose to ovarian tumors and to uterine fibromas. Precocity and exaggerated involution, on the other hand, predispose to cancer.

Geschickter, Lewis and Hartman⁶⁹ concluded that gynecomastia (fig. 5), virginal hypertrophy (fig. 6) and fibro-adenoma are dependent on pathologic variations in the action of estrous hormone on the duct epithelium and surrounding connective tissue of the breast. This form of hypertrophy is easily produced in male animals. The condition is also prevalent in females in the prepubertal period and during the latter two thirds of pregnancy. The findings of Geschickter and co-workers permit a distinction to be drawn between hypertrophy or hyperplasia and true tumor formation. In hypertrophy, such as gynecomastia in the male and virginal hypertrophy in the female, the etiologic factor is an abnormally high concentration of estrin in the circulation acting on apparently normal breast tissue. In the formation of a tumor, on the other hand, for example a fibro-adenoma, the increased amounts of

66. Hofbauer, J.: Leucoplakia Cervicis Uteri and Early Carcinoma, *Am. J. Obst. & Gynec.* **27**:633, 1934.

67. Overholser, M., and Allen, E.: Ovarian Hormones and Traumatic Stimulation of Monkey's Cervix to a Condition Resembling Early Cancer, *Proc. Soc. Biol. & Med.* **33**:1322, 1933.

68. Buzzi, B.: Relation of Ovarian Dysfunction, Hyoplasia, and Hyper-Involution to Tumors of the Female Genitalia, *Folia gynaec.* **29**:339, 1932.

69. Geschickter, C. F.; Lewis, D., and Hartman, C. G.: Tumors of the Breast Related to the Oestrous Hormone, *Am. J. Cancer* **21**:828, 1934.

estrin in the blood act on a hypersusceptible tissue which has the capacity greatly to concentrate the hormone. This is brought about by a basic biologic variation of the developmental response in that particular tissue.

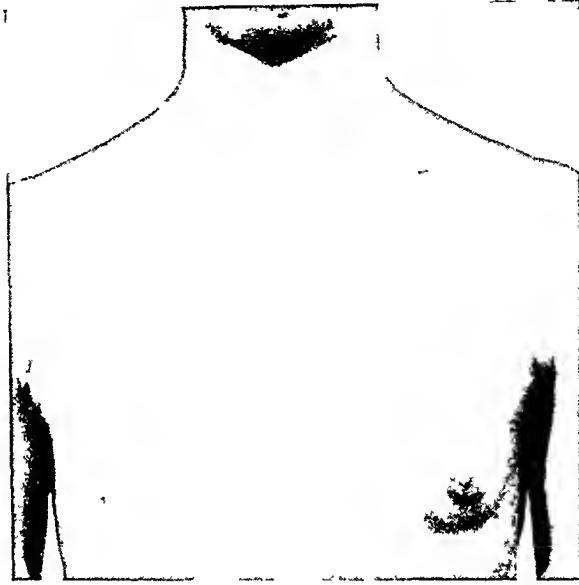


Fig. 5—Bilateral gynecomastia in a colored boy, aged 17, more pronounced on the left side. (Courtesy of Dr. C. F. Geschickter.)



Fig. 6—Bilateral diffuse vaginal hypertrophy in a white woman of 31 years. (Courtesy of Dr. C. F. Geschickter.)

The investigators at Johns Hopkins University, as a result of their work, have shown a relationship of gynecomastia, vaginal hypertrophy, fibro-adenoma, cystic disease and fibrosarcoma to the ovarian hormone estrin. This suggests new methods of diagnosis and treatment of these

conditions. This is done by an assay of the estrin in the blood. A low basal metabolic rate also reveals an increased concentration of estrin in the blood.

Recently Lewis and Geschickter⁷⁰ observed that a fibro-adenoma removed from the breast of a Negro girl yielded forty-five times as much estrin per unit of weight as normal hog ovaries (1 unit per nine grams of tumor).⁷¹

A softening or involution of gynecomastia was obtained by treatment with prolactin, the hormone of the anterior lobe of the pituitary gland which induces the secretion of milk; involution occurred two weeks after the injections were stopped.

The presence of estrin in cancerous areas has also been reported by Silverstein, Fellner and Engel.⁷² Lacassagne⁷³ has reported the appearance, after repeated injections of estrin, of mammary cancer in from 50 to 80 per cent of animals belonging to two strains which normally have an incidence of cancer of only 2 per cent. Thyroxine has also been shown to inhibit tumor growth in experimental animals (Gilroy;⁷⁴ Aub and co-workers⁷⁵).

Prolan.—The results of the aforementioned researches definitely establish that increasing concentrations of estrin are concerned in the production of a certain type of carcinoma, especially that of the mammary glands. It is also well known that the anterior lobe of the pituitary gland contains several important hormones, among which are prolans A, and prolans B, essential for luteinization and the formation of progesterin (Zondek).

Leonard, Meyer and Hisaw⁷⁶ have shown that injections of estrin cause an increase in the weight of the hypophysis. This had been

70. Lewis, D., and Geschickter, C. F.: Estrin in High Concentration Yielded by a Fibro-Adenoma of the Breast, *J. A. M. A.* **103**:1212 (Oct. 20) 1934.

71. Lewis and Geschickter (Gonadotropic and Estrogenic Principles in a Myoma of the Uterus, *J. A. M. A.* **104**:45 [Jan. 5] 1935) stated that a myoma of the uterus assayed 4 units of estrin per gram of tissue, or 1,800 units per pound.

72. Silverstein, F.; Fellner, O. O., and Engel, P.: The Appearance of an Oestrous Producing Substance in the Blood Tissues Under Pathological Conditions, *Ztschr. f. Krebsforsch.* **35**:420, 1932.

73. Lacassagne, A.: Pathogenesis of Mammary Adenocarcinoma in the Mouse, *Compt. rend. Soc. de biol.* **115**:937, 1934; **114**:427, 1933.

74. Gilroy, E.: Comparison of the Effects of Arginine and Thyroxine upon Tumor Growth, *Biochem. J.* **24**:1181, 1930.

75. Meyer, O. O.; McTiernan, C., and Aub, J. C.: The Effect of Thyroxine upon the Metabolism of Isolated Normal and Malignant Tissue, *J. Clin. Investigation* **12**:723, 1933.

76. Leonard, S. L.; Meyer, R. K., and Hisaw, F. L.: The Effect of Oestrin upon the Development of the Ovary in Immature Female Rats, *Endocrinology* **15**:17, 1931.

observed earlier by Halpern and D'Armour,⁷⁷ who found that the hypophysis in male and female castrates given injections of estrin was 100 per cent heavier than that in controls not treated with estrin, while in normal females the weight of the pituitary gland exceeded the weight of this gland in the controls by 200 per cent. This confirms the well known fact that there is a very close physiologic relationship between the internal secretions of the anterior lobe of the pituitary gland and the ovary.

If it is true that increased concentrations of estrin predispose to malignant changes, what effect will injections of a solution of the anterior lobe of the pituitary gland have on cancerous tissue?

Zondek⁷⁸ was the first to show that the urine of patients with malignant tumors contains a hormone similar to that of the anterior lobe of the pituitary gland, especially that of patients with genital carcinoma. This finding has been confirmed by Dodds⁹ and others. Ferguson⁷⁹ studied the excretion of prolان A in the urine in 117 consecutive cases of teratoma testis. This amounted to from 50 to 50,000 mouse units per liter of urine. Local recurrence or metastasis was accompanied by an increase of prolان A in the urine. Observations at autopsy revealed the important relation between the hormone of the anterior lobe of the pituitary gland and epithelial hyperplasia in the genital organs of the male, especially in the prostate and seminal vesicles.

Zondek and co-workers⁸⁰ recently studied the effect of prolان on the growth of the Ehrlich mouse carcinoma. Eighteen hundred mice were used, and the tumors "took" in 100 per cent of the cases. The mice were killed twenty-three days after the injection of prolان, and the tumors were cut and weighed. The average weight of 247 control tumors was 1.65 Gm. The average weight of the tumors of 250 animals which had been treated with thyroxine, epinephrine or folliculin was 1.55 Gm. The average weight of the tumors in 405 mice treated with prolان was only 0.2 Gm.

The effect of prolان has also been observed by other workers. For instance, Moller⁸¹ used 70 male mice weighing from 10 to 12 Gm. and bearing the Ehrlich mouse carcinoma (which does not regress

77. Halpern, S. R., and D'Armour, F. E.: Effects of Oestrin upon Gonads, Mammary Glands and Hypophysis of the Rat, *Proc. Soc. Biol. & Med.* **32**:108, 1924.

78. Zondek, B.: Ueber die Hormone des Hypophysenvorderlappens: III. Follikelreifungshormon (Prolan A) und Tumoren, *Klin. Wchnschr.* **9**:679, 1930.

79. Ferguson, R. S.: Quantitative Behavior of Prolan A in Teratoma Testes, *Am. J. Cancer* **18**:269, 1933.

80. Zondek, H.; Zondek, B., and Werner, H.: Prolan and Tumor Growth, *Klin. Wchnschr.* **18**:137, 1933.

81. Moller, H.: Relation Between Tumor Growth and the Hormone of the Anterior Hypophyseal Lobe, *Am. J. Cancer* **20**:67, 1934.

spontaneously in the strain used). Just before inoculation the animals were divided into two groups: Thirty received no treatment. Forty were given 50 rat units of prolan daily from the first to the tenth day, the dose being then increased to 200 rat units, which was given from the sixteenth to the twenty-second day. The animals were killed on the twenty-third day, and their tumors were removed and weighed. The average weight was 0.22 Gm. as compared with 1 Gm. for the untreated controls. This confirms the work of Zondek with comparable doses. It was also observed (in confirmation of the work of Zondek) that the tumors from the prolan-treated mice were so reduced in vigor of growth as to be no longer transplantable. At autopsy all prolan-treated mice showed the well known enlargement of the generative organs, that is, striking hypertrophy and hyperplasia of both adrenal glands, with the microscopic changes corresponding to pregnancy. This hypertrophy of the adrenal glands Moller believed to be most important. It is possible that prolan stimulates the adrenal cortex to secrete more of a new hormone, which then causes regression of the tumor.

Cannavo⁸² injected prolan into 30 experimental mice in each of two series inoculated with a mouse carcinoma. Thirty mice without injections of prolan were used as controls. Fifteen hundred rat units of prolan caused a retardation in the growth of the tumor in only 2 of 30 animals, but 2,300 units (800 before and 1,500 after inoculation) caused definite and constant retardation. The results of these investigations with prolan have been confirmed by Ludwig and von Ries.⁸³

The evidence presented shows that increased concentrations of estrin favor the production of malignant changes while injections of prolan (possibly by stimulating the adrenal glands with resultant hypertrophy) tend to cause regression of cancerous growth. It is also possible that the loss of prolan in the urine of patients with cancer, as observed by Zondek and others, favors increased production of estrin, with resultant malignant changes. On the other hand, the marked hypertrophy of the pituitary gland following injections of estrin, as observed by Halpern and D'Armour,⁷⁷ may be responsible for the increased excretion of prolan in the urine of patients with cancer. Prolan is then lost to the body, and this possibly creates an imbalance between prolan and estrin favoring the development of malignant growths. While this is mere speculation, it is nevertheless of importance in the future to study this antagonistic relation between prolan and estrin in the development of some types of cancer.

82. Cannavo, L.: Influence of Prolan on the Growth of Inoculated Mouse Carcinoma, *Riforma med.* **49**:278, 1933.

83. Ludwig, F., and von Ries, J.: Hormone, Vitamine, Zellwachstum und Karzinom, *Schweiz. med. Wchnschr.* **64**:141, 1934.

Extracts of Testicle, Spleen, Thymus and Parathyroid Gland and Placenta.—Hoffman, Parker and Walker⁸⁴ stated that extract of rabbit testicle markedly enhanced the growth of chicken tumor I. These results were obtained when tumor mash or cell-free filtrates were used in the inoculations. Duran-Reynals and Claude⁸⁵ confirmed these results. They showed that the agent of chicken tumor I was spread when it was injected together with an extract of testicle, and that the resultant lesions were greatly enhanced. On the other hand, Duran-Reynals⁸⁶ showed that an extract of rat, rabbit or bull testicle prevents or retards the growth of a rabbit tumor when a mixture of the extract and a suspension of the tumor cells is inoculated intradermally. Similar mixtures made with normal rabbit serum instead of extract of testicle greatly enhanced the growth of the tumors.

Matsuoka⁸⁷ observed that splenectomy favored the growth of the Kato rabbit sarcoma. In the absence of the spleen the glycolytic activity of the neoplasm was augmented. Treatment with various preparations of spleen inhibited more or less the growth of this sarcoma. Fischera⁸⁸ recently observed that certain organs (spleen, bone marrow, thymus) or their extracts are inimical to tumor growth, whereas others (testes, ovary) are especially favorable. Murphy and Sturm⁸⁹ showed that

Extracts of desiccated homologous embryo skin and placenta decrease markedly the rate of postoperative local recurrence after the surgical removal of spontaneous cancer of mice. Autografts after a short period of contact with these extracts either failed to grow, or, in the majority of instances, their subsequent growth was definitely retarded. Intraperitoneal injection of the extracts was followed by cessation of growth of established tumors in more than two-thirds of the animals treated, and among these many of the tumors regressed and over 20 per cent were completely absorbed. Tumor mice treated with either extract rarely developed new malignant foci, though this happened frequently in untreated mice.

84. Hoffman, D. C.; Parker, F., and Walker, T. T.: Effect of Testicle Extract on Rous Sarcoma, *Am. J. Path.* **7**:523, 1931.

85. Duran-Reynals, F., and Claude, A.: Further Experiments on the Effect of Testicle Extract on the Agent of Chicken Tumor I, *Proc. Soc. Exper. Biol. & Med.* **32**:67, 1934.

86. Duran-Reynals, F.: The Effect of Testicle Extract and of Normal Serum on the Transplantable Epithelial Tumor of the Rabbit, *J. Exper. Med.* **54**:493, 1931.

87. Matsuoka, H.: Effect of Spleen on the Growth of Transplanted Tumor, *Jap. J. Obst. & Gynec.* **17**:25, 1934.

88. Fischera, G.: Significance for Tumor Genesis of Disturbances in Organ Equilibrium and Organotherapy for Malignant Neoplasms, *Klin. Wchnschr.* **12**: 1957, 1933.

89. Murphy, J. B., and Sturm, E.: The Effect of a Growth Retarding Factor from Normal Tissues on Spontaneous Cancer in Mice, *J. Exper. Med.* **60**:305, 1934.

Maigin⁹⁰ also observed a good prophylactic effect following the use of placenta in the form of a fresh graft or of an injected extract with surgical, roentgen and radium treatment. Of 30 patients treated, 10 were still living after five years, while the other 20 were patients recently treated. While it is difficult to judge whether the beneficial effects here were due to surgical, roentgen, radium or placental treatment, nevertheless, at the present time, the use of endocrine products in addition to these other means of treatment in some types of carcinoma is more than justified. Maisin⁹¹ observed that organotherapy (brain, thymus and spleen) had an active inhibitory effect on the course of tar cancers. Maisin, Pourbaix and Picard⁹² observed that ethereal extracts of spleen, brain, thymus and liver, when injected subcutaneously, had an inhibitory effect on the neoplasms of animals and man. The animal tumors were spontaneous mammary carcinomas of the mouse, tar cancers of the mouse and rabbit and a carcinoma of the mamma of the dog. In the human patients the metastasizing carcinomas or sarcomas were beyond the hope of cure by surgical or radium treatment.

Gwyer⁹³ was probably the first to use dried thymus gland in the clinical treatment of cancer. This therapy was found to diminish or eliminate pain, lessen the size of the growth and improve greatly the metabolic condition of the patient. In his second study⁹⁴ the thymus treatment was given to 16 patients with inoperable, incurable and hopeless cancers of various types.

Gwyer summarized his findings as follows:

The foregoing histories of cancer cases present several prominent points, *viz.*

1. With the exception of two or three cases all showed temporary improvement in that there was (a) less pain, (b) reduction in growth, (c) general condition better. This improvement was quite prompt in making its appearance.
2. Several of the patients died or at present are near their end.
3. Many of those that died did not succumb as the cancer patient ordinarily does, in that (a) there was no great loss in weight, (b) no leaden pallor and other visible signs of cachexia, and (c) no local increase of the cancer. On the other hand, at least two of the fatal cases continued fairly well nourished, with

90. Maigin, A. C.: New Treatment of Cancer, *Bull. Soc. d'obst. et de gynec.* **20**:316, 1932.

91. Maisin, J.: Organotherapy by Mouth in Experimental Cancer, *Compt. rend. Soc. de biol.* **107**:916, 1931.

92. Maisin, J.; Pourbaix, Y., and Picard, E.: Experiments on Organotherapy of Cancer by Subcutaneous Injection, *Compt. rend. Soc. de biol.* **107**:918, 1931.

93. Gwyer, F.: Thymus Gland Treatment of Cancer: A Preliminary Report with Presentation of a Case of Inoperable Cancer with Great Relief of Symptoms, *Ann. Surg.* **46**:89, 1907.

94. Gwyer, F.: On the Thymus Gland Treatment of Cancer, *Ann. Surg.* **47**:506, 1908.

clear skin, red mucous membranes, and an actual and marked reduction of the cancer growth, with no evidence of metastases. The same is true of some still living.

Hanson⁹⁵ treated 4 patients who had inoperable carcinomas with daily injections of thymus extract. Definite improvement was observed, with necrosis and absorption of part of the tumors.

Recently Rowntree, Clark and Hanson⁹⁶ reported some remarkable results obtained on the growth of succeeding generations of rats by treating the parent rats with Hanson's thymus extract. Table 2, taken from their paper, gives these results.

The number and size of the litters and the weight at birth increased very greatly in these cases. The third generation of rats whose parents were treated with thymus extract were much larger at birth and showed striking precocity in growth and development, early eruption of teeth,

TABLE 2.—*Development of Thymus-Treated Rats Contrasted with That of Controls (from Rowntree, Clark and Hanson⁹⁶) **

	Controls	F ₁	F ₂	F ₃	F ₄
Average weight at birth, Gm.†.....	4.6	5.1	5.3	5.3	5.3
Ears opened, days.....	2½-3½	2	1-2	1	1
Teeth erupted, days.....	8-10	1-9	1-2	1	1
Hair appeared, days.....	12-16	3-12	4-6	4-5	2-3
Eyes opened, days.....	14-17	12-14	4-6	4-6	2-3
Testes descended, days.....	35-40	†15-29	†5-21	†5-12	4.5
Vagina opened, days.....	55-62	†30-45	†23-32	†21-27	18-19

* The figures in this table are based on a somewhat different setup compared with those published in Seience and in the detailed paper, which will appear later.

† The low numbers usually refer to late litters in the generation and the high numbers to the first litters born.

appearance of the fur, opening of the eyes, descent of the testes and opening of the vagina. It is therefore evident that thymus extract is by far the most active growth-promoting hormone known. This discovery opens a new field for the investigation of problems related to growth.

Inuzuka⁹⁷ showed that parathyroid hormone when injected into rabbits bearing sarcoma and carcinoma inhibited the growth of these tumors. A partial extirpation of the parathyroid glands increased the rate of growth of the tumors. The effect of total parathyroidectomy could not be determined accurately, owing to the development of tetany.

95. Hanson, A. M.: The Bovine Thymus, Minnesota Med. **13**:17, 1930; Treatment of Cancer with Thymus Extract, Correspondence, J. A. M. A. **94**:653 (March 1) 1930.

96. Rowntree, L. G.; Clark, J. H., and Hanson, A. M.: The Biological Effects of Thymus Extract (Hanson), J. A. M. A. **103**:1425 (Nov. 10) 1934.

97. Inuzuka, A.: On the Influence of the Parathyroid Glands upon the Development of Malignant Tumors, Tr. Jap. Path. Soc. **23**:680, 1933.

Paik,⁹⁸ on the other hand, found that the internal secretion of the parathyroid glands stimulated the growth of rat carcinoma, while decrease of this secretion interfered with the development of carcinoma. These results are difficult to reconcile with those of Inuzuka, but it is possible that the parathyroid hormone affects the growth of the tumor either favorably or unfavorably.

Insulin.—After Warburg² and others had shown that there is a defect in the metabolism of carbohydrate in cancer, it was reasonable to expect that insulin might have a beneficial effect on certain types of malignant tissue. This possibility has been realized.

Da Costa⁹⁹ observed that the local application of insulin caused a regression in the growth of skin cancer. Lambret and Driessens¹⁰⁰ observed the complete disappearance of Jensen rat sarcoma in 30 of 40 cases under the influence of insulin injected after the tumors were grafted. Kawamura and Kamikawa¹⁰¹ inhibited the production of tar tumors by injections of insulin, but injections of epinephrine enhanced their production. Konsulov and Dimitrakov¹⁰² inhibited the growth of spontaneous tumors and of Ehrlich's mouse tumor in those in whom it was grafted, with injections of insulin. Further work with insulin in this connection will be awaited with much interest.

Extracts of Adrenal Cortex.—Although several investigators have obtained negative results with extracts of adrenal glands in the treatment of experimental tumors of animals, other workers have obtained positive results. While it is difficult in this connection to judge negative results, it should not be forgotten that the variability in different types of tumors, in animals and in human beings and, most important of all, the variability in the potency of extracts are factors that should be evaluated before negative results are accepted. The activity of hormones can easily be destroyed if the details of the technics for their preparation are not followed closely. Again, an extract that is effective in one patient may not be effective in another with an identical type of

98. Paik, T. S.: On the Relationship Between the Parathyroid Hormone and the Growth of Rat Carcinoma, *Am. J. Cancer* **15**:2756, 1931.

99. da Costa, F. G.: Effect of Insulin on Carbohydrate Metabolism in Cancer of Skin, *Compt. rend. Soc. de biol.* **107**:85, 1931.

100. Lambret, O., and Driessens, J.: Regression and Disappearance of Jensen Sarcoma under the Influence of Insulin Injected after Grafting, *Compt. rend. Soc. de biol.* **112**:1430, 1930; **116**:1068, 1934.

101. Kawamura, M., and Kamikawa, Y.: Relation Between the Production of Tar Tumors and the Organs of Internal Secretion Which Have a Special Relation to the Metabolism of Carbohydrate, *Am. J. Cancer* **15**:2835, 1933.

102. Konsulov, S., and Dimitrakov, K.: The Cancer Problem as a Hormone Problem, *Am. Univ. Sofia Facult. phys.-math.*, 1933, vol. 28, no. 3; *Ztschr. f. Krebsforsch.* **36**:37, 1932.

carcinoma. An extract of a certain gland should not be expected to be effective in a certain type of tumor if there is no physiologic connection between the gland and the structure in which the tumor is growing.

For example, extracts of adrenal cortex should be expected to exert their best effect on carcinomas and sarcomas of the reproductive system (the breast excepted) and the urogenital system, rather than on those of the tongue and face. Again, the lactation-promoting hormone of the anterior lobe of the pituitary gland, prolactin, would be expected to affect the growth of mammary tumors. Also a transplantable tumor in an animal with a normal endocrine system may or may not be the same as, for instance, a carcinoma of the cervix in a woman whose endocrine system may or may not be normal. These and many other factors add to the uncertainty of negative results. Until the hormones are isolated in a chemically pure state and their effects on the growth of tumors are observed by a number of different workers, we may expect differences of opinion as to their value or nonvalue in different experimental and clinical conditions.

This confused state of affairs, however, is no justification for abandoning endocrine therapy in malignant conditions. The best procedure at present is simply to record the results obtained and evaluate these some time in the future when more data are available.

Boris Sokoloff¹⁰³ was the first to publish data on the beneficial effects of extracts of the cortex of the adrenal gland (fortified with iron and tri-naphthyl-para-rosanalin sulphate) on tumors. Working at the Rockefeller Institute for Medical Research in 1928, he noticed that in cancerous chickens the cortex of the adrenal gland grew to five times its normal size. The cortex was also very sensitive to the malignant neoformations. Later, at the meeting of the International Physiological Congress in Boston in 1929, he gave a demonstration of the liquefaction of malignant tumors with this extract. The mice and rats were the bearers of four kinds of tumors: rat sarcoma no. 10, rat sarcoma no. 39, mouse sarcoma no. 180 and F. R. sarcoma. All these animals were from the stock of the Institute for Cancer Research of Columbia University. About 1,000 experiments were performed. It was observed that the process of liquefaction began very rapidly: In small tumors sclerosis set in within from three to five days. Larger tumors dissolved in about two weeks. Rapid liquefaction caused the death of some of the animals.

103. Sokoloff, B.: Physiological Studies of Malignant Cells: Preliminary Communication, abstr., Proc. Internat. Physiol. Congress, 1929, p. 251; Studies on the Adrenal Cortex: I. Changes in the Adrenal Cortex and Its Reticulo-Endothelial Cells Under the Influence of Transplanted Tumors, Arch. f. exper. Zellforsch. **11**:112, 1931; II. Liquefaction of Malignant Tumors, *ibid.*, p. 114.

This important work of Sokoloff, which attracted little attention at the Congress, has since been confirmed by several other workers. Auler and Rubenow¹⁰⁴ prepared an extract from the adrenal cortex which when injected into rats bearing the Jensen sarcoma or the Flexner-Jobling carcinoma caused regression in the tumors in a certain number of animals. Arloing, Morel, Josserand and Badinand¹⁰⁵ found that injections of a protein precipitate from glycerin extracts of calves' adrenal glands greatly inhibited the growth of an experimental mouse tumor. Vassiliadis¹⁰⁶ prepared an ether-acetone extract of adrenal glands and hypophysis, to which an alcoholic solution of magnesium chloride was added. The precipitate was collected and suspended in water, and a dose equivalent to 0.5 Gm. of fresh tissue was injected into mice which were receiving applications of tar. Only 40 per cent of the mice thus treated had developed tumors at the end of two hundred and forty days, while 100 per cent of the controls, treated only with tar, had developed tumors. The antiblastic substance was also stated to occur in brain, bone marrow, thymus and other tissues. Sano¹⁰⁷ observed that treatment with testicle and adrenal gland had an inhibitory influence on the growth of the Fujinami chicken myxosarcoma in vitro. Vles, de Coulon and Ugo¹⁰⁸ observed that the feeding of adrenal gland, testicle and digestive tube produced a considerable decrease in the incidence of cancer produced by tar in experimental animals.

Arloing, Josserand and Charachon¹⁰⁹ observed an inhibition of the growth of a mouse carcinoma after the subcutaneous transplantation of the adrenal gland from a rabbit prepared by inoculations of the same tumor. A glycerin extract was equally effective. Arloing¹¹⁰ observed

104. Auler, H., and Rubenow, W.: Relation Between the Adrenals and Neoplastic Growth, *Ztschr. f. Krebsforsch.* **33**:292, 1930.

105. Arloing, F.; Morel, A.; Josserand, A., and Badinand, A.: Further Studies on the Tumor Inhibiting Properties of Adrenal Extracts Tested on Experimental Epithelioma in White Mice, *Compt. rend. Soc. de biol.* **112**:156, 1933.

106. Vassiliadis, H.: Existence of Antiblastic Substances in the Adrenals and Hypophysis, *Compt. rend. Soc. de biol.* **115**:1241, 1934.

107. Sano, A.: The Influence of Hormones on the Growth of Transplantable Chicken Myxo-Sarcoma Cultivated in Vitro, *Tr. Jap. Path. Soc.* **21**:805, 1931.

108. Vles, F.; de Coulon, A., and Ugo, A.: Investigations on the Physico-chemical Properties of Tissues in Relation to the Normal or Pathological State of the Organism: XVII. Recent Studies on the Statistical Evolution of Cancer as Caused by Tarring, *Arch. de phys. biol.* **10**:304, 1933.

109. Arloing, F.; Josserand, A., and Charachon, J.: Modifications évolutives de l'épithélioma expérimental de la souris blanche par greffes de surrénales provenant de lapins préparés avec ce même épithélioma, *Compt. rend. Soc. de biol.* **100**:1035, 1929.

110. Arloing, F.: Further Investigation of Retarding Action of Suprarenal Extracts on Transplantable Mouse Carcinoma, *Am. J. Cancer* **19**:406, 1933.

that an extract of calves' adrenal glands contained an agent capable of retarding the growth of a transplantable mouse carcinoma. The average weight of the tumors in the treated animals was 0.73 Gm., whereas in the untreated controls it was 4.04. Gm.

The foregoing evidence justifies the view that, contrary to the opinion of many workers, the adrenal gland contains an anticarcinogenic substance. From my chemical work on an active extract of adrenal gland I am convinced that the anticarcinogenic substance here is different from the cortical hormone of Swingle and Pfiffner and others. This view is based on the difference in the chemical properties of the two hormones. This fact shows that it would be unprofitable to use the cortical hormone in the clinical treatment of malignant conditions.

SULPHYDRYL COMPOUNDS

At the present time biochemists are showing much interest in the metabolism of oxidized and reduced sulphur compounds as cystine, cysteine, methionine, glutathione, insulin and the posterior pituitary hormones. It has long been known that proteins containing organic sulphur, as in cystine and methionine, are the chief sources of sulphur in metabolism, and that organic sulphur is necessary for growth. In this country the chief workers in this important field at the present time are Lewis, Sherwin, Brand, Voegtlin, Sullivan, du Vigneaud, Hammett and their coworkers, most of whom read interesting papers in a symposium on sulphur metabolism before Section N of the American Association for the Advancement of Science at the recent meeting in Pittsburgh. Hammett ¹¹¹ and Reimann and Hammett ¹¹² discussed the importance of sulphydryl ($-\text{SH}$) ¹¹³ from both the physiologic and the pathologic point of view, and are now using sulphydryl compounds to bring about healing of long-standing ulcers and bedsores which have hitherto resisted all therapeutic effort.

111. Hammett, F. S.: *Natural Chemical Factors in Growth and Development: Symposia on Quantitative Biology*, Long Island, N. Y., Cold Spring Harbor Biological Laboratory, 1934, vol. 2, p. 78.

112. Reimann, S. P., and Hammett, F. S.: *Cell Proliferation Response to Sulphydryl in Man*, *Proc. Soc. Exper. Biol. & Med.* **27**:20, 1929.

113. Sulphydryl ($-\text{SH}$) is the name given to the reduced sulphur group of cysteine, two molecules of which are supposed to be formed in the metabolism of a molecule of the amino-acid cystine in the body, as follows:



Some seven years ago Hammett¹¹⁴ and co-workers began their extensive studies on factors that control normal and pathologic growth. They desired to know whether lead, which Blair Bell had already reported to be a retardant of embryonic growth, was an inhibitor of growth with regard to cell number or with regard to cell size or assimilation. The results of their work showed that lead inhibits cell growth in number rather than in size. This fact gave rise to the view that lead removes some chemical entity essential to multiplication. Further work showed that the precipitate consisted of lead with an unoxidized sulphur group—ing similar to that in glutathione, which presumably was sulphhydryl. This reduced sulphur compound is present in largest amounts where mitosis is most active. Thus it seems probable that lead, by precipitation of the sulphhydryl, may inhibit cell division. Toennies recently prepared some suboxidized derivatives of cysteine which, according to Hammett and Hammett,¹¹⁵ comprise a naturally occurring chemical equilibrium which is specifically essential to the regulation of the proliferative phase of developmental growth.

According to Hammett,¹¹⁶ the relationship of these findings to the problem of cancer depends entirely on the significance of proliferation to malignant growth, with especial emphasis on those factors which are conducive to malignant growth. It was shown that the potential proliferation of immature cells is greater than that of more mature cells, and that immature cells are more sensitive to the action of sulphhydryl, which is found in high concentration where cell division is most active. Hammett expressed the belief that control of the proliferative phase of cancer can be obtained (1) by discovering ways of decreasing the sulphhydryl content of tumor tissue or (2) by introducing the partially oxidized derivatives (sulphoxides) of the accelerating ($-SH$) groups. He summarized the matter as follows:

From what has gone before it would seem that a partial solution of the cancer problem rests upon the discovering of naturally occurring chemical factors determinative of cell maturity. Towards this an attempt has been under way for the past three years to ascertain whether or not any of the amino acids and nucleic acid derivatives have any specific influence upon any particular developmental activity. Results have been obtained which are in press. The work is still in progress and probably will be for many years to come.

114. Hammett, F. S.: The Influence of Sulphydryl on Cell Proliferation and Its Possible Significance in the Cancer Problem. Paper read in the Symposium on Sulfur Metabolism, Sect. N, American Association for the Advancement of Science, in Pittsburgh, Dec. 29, 1934.

115. Hammett, D. W., and Hammett, F. S.: Crucial Demonstration of the Proliferative Growth Regulating Property of the Naturally Occurring Chemical Equilibrium Composed of Sulphydryl and Its Partially Oxidized Derivatives, *Protoplasma* **19**:161, 1933.

116. Hammett, F. S.: Cancer as a Problem in the Biology of Cell Division, *Tr. Coll. Physicians, Philadelphia* **54**:136, 1932. Hammett,¹¹⁴

SUMMARY

Cancer as a problem in metabolism has been reviewed under the following headings: carbohydrate metabolism of tumors; lipid metabolism and cholesterol; irradiation and carcinoma of the skin; the carcinogenic hydrocarbons.

Endocrine imbalance in the pathogenesis of some types of cancer was reviewed under headings as follows: estrin; prolan; extracts of testicle, spleen, thymus and parathyroid gland; insulin; extracts of adrenal cortex.

While it is difficult at present to distinguish cause and effect in the newer experimental work on cancer reviewed in this paper, the following concepts are worthy of serious consideration by students of the problem.

1. In malignant tumors the metabolism of carbohydrate is abnormal, resulting in low respiration and high glycolysis.

2. Lipoids and cholesterol are definitely increased, the latter especially in carcinoma of the skin.

3. Massive doses of ultraviolet radiation may produce cancerous lesions about the eyes, ears and head of the experimental animal.

4. Hydrocarbons containing the phenanthrene group and estrin are both carcinogenic and estrogenic.

5. The chemical relationship of the bile acids, sterols, sex hormones and carcinogenic hydrocarbons is established.

6. Injections of prolan may inhibit the growth of some types of tumors.

7. Extracts of adrenal cortex, thymus and spleen and insulin may also have a retarding influence on some types of experimental tumors.

8. The relation of sulphhydryl ($-SH$) to the problem of cancer was discussed.

Dr. F. S. Hammett of the Lankenau Hospital Research Institute of Philadelphia allowed me to summarize, in advance of publication, his recent paper, "The Influence of Sulphydryl on Cell Proliferation and Its Possible Significance in the Cancer Problem," read before Section N of the American Association for the Advancement of Science recently in Pittsburgh.

BACTERIOLOGY OF NORMAL AND DISEASED GALLBLADDERS

EDMUND ANDREWS, M.D.

AND

LUCY DELL HENRY, M.D.

CHICAGO

Previous studies of the flora of diseased gallbladders have revealed the presence of a wide variety of micro-organisms. One school has placed the blame for cholecystitis on organisms of the colon bacillus group, which grow so rapidly in bile. Most writers of the older literature take this attitude. On the other hand modern observers and especially experimenters are inclined to implicate the streptococcus, which is also a common inhabitant of the gallbladder. Rosenow,¹ Wilkie² and Magner and Hutcheson³ have reviewed the recent literature on this subject and made significant contributions. It seems undoubtedly true that experimental cholecystitis is best produced by the streptococcus.

However, since the time of Osler⁴ a significant point has received but little attention, namely, the fact that even in the presence of severe pathologic damage to the gallbladder the bile or fluid contents are sterile in a large majority of cases. Osler reported sterile findings in 52 per cent of the cases. More recent studies have materially increased this figure. Magner and Hutcheson's review of the American literature shows a tabulation of the results in 1,340 cases from thirteen different clinics; in 65 per cent of the cases sterile contents were found. This (65 per cent) is the exact incidence found in our own studies. Usually the wall of the gallbladder has yielded bacteria about twice as frequently as the contents, which fact may be explained on the basis of lymphoid tissue in and around the wall of the gallbladder especially near the

From the Department of Surgery, University of Chicago.

1. Rosenow, E. C.: *The Etiology of Cholecystitis and Gallstones and Their Experimental Production by the Intravenous Injection of Bacteria*, J. Infect. Dis. **19**:527, 1916.
2. Wilkie, A. L.: *The Bacteriology of Cholecystitis*, Brit. J. Surg. **15**:450, 1928.
3. Magner, W., and Hutcheson, J. M.: *Cholecystitis*, Canad. M. A. J. **17**:469, 1932.
4. Osler, W.: *Modern Medicine*, Philadelphia, Lea Brothers, 1907.

ducts. The fact has been overlooked by many that the lymphoid tissue is one of the chief filter basins in the body for foreign material; hence it tends to concentrate the bacteria more in the wall than in the bile.

In view of these facts it was felt that in order to elucidate the relationship of bacteria to disease of the gallbladder, more detailed studies were necessary. One must know not only the type of bacteria but their number. The intimate relation of the gallbladder to the intestine with its rich flora and the close lymphatic connection between the two have been emphasized by Graham and Peterman.⁵ Furthermore, the fact that flora of the normal liver is surprisingly rich (as revealed by the work of Ellis and Dragstedt,⁶ Andrews and Hrdina,⁷ Andrews, Rewbridge and Hrdina,⁸ Berg, Faw and Jobling,⁹ Dvorak¹⁰ and others) also emphasizes the fact that the gallbladder lies in a far from sterile locale and that in order to attribute pathogenicity to any bacteria found it must be shown that they exist in numbers compatible with the recognized conception of a true infection. All the authorities emphasize the fact that the gallbladder is a favorite lurking place for bacteria (Osler,⁴ Kaufmann,¹¹ Rolleston and McNee¹² and Graham and his co-workers¹³). These organisms do not necessarily cause infection. This point will be discussed in greater detail later but is mentioned to show the necessity of knowing something quantitative about the flora of the gallbladder in different stages of activity or quiescence.

5. Graham, E. A., and Peterman, M. G.: Further Observations on the Lymphatic Origin of Cholecystitis, Cholelithiasis and the Associated Pancreatitis, *Arch. Surg.* **4**:23 (Jan.) 1922.

6. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis in Vivo, *Arch. Surg.* **20**:8 (Jan.) 1930.

7. Andrews, E., and Hrdina, L.: (a) Cause of Death in Liver Autolysis, *Surg., Gynec. & Obst.* **52**:61, 1931; (b) Hepatogenous Cholecystitis, *Arch. Surg.* **23**:201 (Aug.) 1931.

8. Andrews, E.; Rewbridge, A. G., and Hrdina, L.: Causation of *Bacillus Welchii* Infection in Dogs by Injection of Sterile Liver Extracts or Bile Salts, *Surg., Gynec. & Obst.* **53**:176, 1931.

9. Berg, B. N.; Faw, F. D., and Jobling, J. W.: Bactericidal Function of the Liver, *Proc. Soc. Exper. Biol. & Med.* **24**:433, 1927.

10. Dvorak, H. J.: Liver Autolysis in the Peritoneal Cavity of Dogs, *Proc. Soc. Exper. Biol. & Med.* **29**:431, 1932.

11. Kaufmann, Edward: Pathology for Students and Practitioners, Philadelphia, P. Blakiston's Son & Co., 1929.

12. Rolleston, H. D., and McNee, J. W.: Diseases of Liver, Gall-Bladder and Bile Duct, New York, The Macmillan Company, 1929.

13. Graham, Evarts Ambrose; Cole, Warren H.; Copher, Glover H., and Moore, Sherwood: Diseases of the Gall-Bladder and Bile Duct, Philadelphia, Lea & Febiger, 1928.

METHODS

The material reported on consists of cultures made on ninety-one gallbladders and their contents removed surgically at the clinics of the University of Chicago.

Immediately after removal from the abdominal cavity the intact gallbladder was placed in a sterile specimen container, covered and taken to the laboratory. Within a short time the bile was aspirated through the wall with a sterile needle and syringe and placed in a sterile test tube. Then, with sterile scissors and forceps, 1 or 2 Gm. of tissue was removed, usually from the fundus of the gallbladder, placed in sterile mortar with sand and saline solution and ground vigorously. This macerated piece of tissue with the saline solution was then cultured in a deep brain tube, the tissue being placed well below the surface of the brain, thus giving an ideal condition for growth of both aerobic and anaerobic organisms. The bile was cultured not only in the deep brain tube but also on a blood agar plate, and 0.1 cc. of bile was placed in a poured agar plate. The latter procedure was carried out for the purpose of estimating the number of organisms per cubic centimeter of bile. Thus a quantitative estimation of the infection in the bile was obtained. The plates were incubated for seventy-two hours before being labeled "no growth." The brain tubes were examined each day for the first five days, smears being made which were stained by Gram's method and searched for organisms; at the same time transfers were made from the brain tubes to the surface of blood agar plates. After the fifth day the tubes were examined every two or three days, and no tube was discarded as sterile before twenty-one days had elapsed.

All organisms isolated were identified by standard bacteriologic procedures. Thus in the bile definite counts could be made in most cases. However, in cases in which anaerobes were found a quantitative estimation was not made, as anaerobic plates were not made on the original bile.

The ninety-one gallbladders were classified into five groups (tables 1 to 5): Group 1 comprised normal gallbladders. This classification was based on the histologic and gross picture. Some patients whose gallbladders were included in this series had had fairly typical biliary colic, and one had had jaundice, but in all the disease had been quiescent for long periods when the operation was performed. Group 2 comprised normal gallbladders with stones; group 3, gallbladders from patients with obstruction of the common duct, and groups 4 and 5, gallbladders from patients operated on in the active and quiescent stages of the disease, respectively. The gallbladders in groups 4 and 5 were classified wholly on the basis of the clinical symptoms; all showed varying degrees of pathologic change, and nearly all contained stones. Those from patients operated on in the active stage included all those obtained at operation performed within five days of a typical biliary colic. Those from patients operated on in the quiescent stage were from patients who had been free from symptoms for more than five days before operation; many were from patients who had been symptomless for long periods. Some patients had never had attacks of colic, the diagnosis having been made by roentgen examination.

ANALYSIS OF RESULTS

A general survey of results is given in table 6. It can be seen at once that our figures correspond in a rough way with those of previous investigators. In about two thirds (67 per cent) of the cases the bile

TABLE 1.—*Results of Cultures of Normal Gallbladders*

Number	Wall	Bile	Colonies per Cc.
1	Sterile	Sterile	
2	Sterile	Sterile	
3	Staphylococcus albus	Sterile	
4	Gram-negative spore former	Gram-negative spore former	5
5	Sterile	Sterile	
6	Bacillus Welchii	Sterile	
7	Sterile	Sterile	
8	Sterile	Sterile	

TABLE 2.—*Results of Cultures on Normal Gallbladders Containing Stones*

Number	Wall	Bile	Colonies per Cc.
1	Bacillus Welchii	Sterile	
2	Bacillus coli, staphylococci	Bacillus coli, staphylococci	350
3	Gram-positive diphtheroids	Gram-positive diphtheroids	2,610
4	Sterile	Sterile	
5	Streptococcus viridans	Streptococcus viridans	50,000
6	Sterile	Sterile	
7	Bacillus Welchii	Bacillus Welchii	
8	Sterile	Sterile	
9	Sterile	Sterile	
10	Few diphtheroids and streptococci	Sterile	
11	Sterile	Sterile	
12	Staphylococci albus (few)	Sterile	

TABLE 3.—*Results of Cultures of Gallbladders from Patients with Obstruction of the Common Duct*

Number	Diagnosis	Wall	Bile	Colonies per Cc.
1	Stone	Bacillus coli, Bacillus Welchii	Bacillus coli, Bacillus Welchii	Innumerable
2	Portal suppuration	Bacillus coli	Innumerable
3	Stone, quiescent	Bacillus coli, Bacillus Welchii	Bacillus coli, Bacillus Welchii	Innumerable
4	Carcinoma of pancreas	No culture made	Bacillus coli, Bacillus Welchii	Innumerable

proved to be sterile, while 51 per cent of the cultures from the walls were found to be sterile (table 8). It has been assumed by several previous investigators³ that the finding of staphylococci represented contaminations due to the handling of the tissues in grinding. If this view were adopted it would considerably increase the percentage of

TABLE 4.—Results of Culture of Gallbladder from Patients Operated on During Quiescent Stage of Disease

Number	Wall	Bile	Colonies per Cc.
1	Sterile		
2	Few staphylococci	Sterile	
3	Sterile	Sterile	
4	Sterile	Sterile	
5	Sterile	Sterile	
6	Bacillus coli	Sterile	
7	Sterile	Bacillus coli	
8	Bacillus typhosus	Sterile	
9	Sterile	Sterile	Innumerable
10	Staphylococcus aureus	Sterile	
11	Sterile	Sterile	
12	Sterile	Sterile	
13	Sterile	Sterile	
14	Sterile	Sterile	
15	Sterile	Sterile	
16	Bacillus coli	Sterile	
17	Sterile	Sterile	
18	Sterile	Bacillus coli	
19	Streptococcus viridans, staphylococci	Sterile	
20	Sterile	Bacillus Welchii	
21	Sterile		
22	Staphylococci, Bacillus Welchii	Sterile	
23	Sterile	Sterile	
24	Sterile	Streptococci	
25	Bacillus coli	Staphylococci	50
26	Sterile	Micrococcus flavus	Few
27	Diphtheroids	Bacillus coli	
28	Few anaerobic streptococci	Sterile	
29	Few streptococci, staphylococci	Diphtheroids	Innumerable
30	Few streptococci, staphylococci	Sterile	
31	Sterile	Sterile	88
32	Sterile	Streptococci, staphylococci	
33	Bacillus subtilis (few)	Sterile	Few
34	Staphylococci	Sterile	
35	Gram-negative rods	Sterile	
36	Sterile	Gram-negative rods	Innumerable
		Sterile	

TABLE 5.—Results of Cultures of Gallbladders from Patients Operated on During Active Stage of Disease

Number	Wall	Bile	Colonies per Cc.
1	Staphylococci; Bacillus coli		
2	Staphylococcus albus	Staphylococci; diphtheroids; Bacillus coli	
3	Sterile	Staphylococcus albus	Innumerable
4	Sterile	Sterile	
5	Sterile	Sterile	
6	Gram-negative spore former	Sterile	
7	Sterile	Gram-negative spore former	
8	Sterile	Staphylococci	25
9	Sterile	Sterile	100
10	Sterile	Sterile	
11	Sterile	Sterile	
12	Bacillus coli	Sterile	
13	Streptococci	Bacillus coli	
14	Staphylococci	Streptococci	Innumerable
15	Bacillus coli (many)	Staphylococci	
16	Sterile	Bacillus coli	Few
17	Sterile	Sterile	
18	Sterile	Sterile	
19	Staphylococci and Bacillus Welchii	Staphylococci and Bacillus Welchii	
20	Sterile	Sterile	
21	Sterile	Sterile	
22	Anaerobic spore former (not Bacillus Welchii)	Sterile	1,500 (staphylococci)
23	Anaerobic Streptococcus haemolyticus	Sterile	
24	Bacillus Welchii	Anaerobic Streptococcus haemolyticus	
25	Sterile	Bacillus coli	
26	Few staphylococci	Sterile	
27	Sterile	Sterile	100
28	Sterile	Sterile	
29	Streptococci (many)	Sterile	
30	Bacillus coli	Streptococci	
31	Sterile	Bacillus coli	
		Sterile	1,000

gallbladders from which it proved impossible to culture bacteria. However, this does not seem to us to be a reasonable assumption, as the percentage of staphylococci found appears to be the same as the figure for several other organisms and, furthermore, it is possible to produce cholecystitis experimentally by the injection of staphylococci.¹⁴ Moreover, in experimental cholecystitis produced by ligating the cystic duct or ligating the cystic artery the staphylococcus is not an uncommon invader along with the other organisms found.^{7b} It seems unnecessary, then, to discriminate against this organism any more than against any other found in similar numbers.

The main point is to note the number of instances in which either the bile or the gallbladder wall was sterile. The interpretation of this phenomenon is difficult. Some have regarded the bactericidal powers of the bile as a satisfactory explanation. This appears to us to be

TABLE 6.—*Summary of Data Given in Tables 1 to 5*

Result	Wall		Fluid	
	Number	Percentage	Number	Percentage
Sterile (including diphtheroid bacilli* and <i>Bacillus subtilis</i>).....	51	57	61	67
Staphylococci.....	13	14	8	9
Streptococci.....	8	9	6	7
<i>Bacillus coli</i>	10	11	14	16
<i>Bacillus Welchii</i>	10	11	8	9
Typhoid bacilli.....	1	1	1	1

* It may be questionable to ignore diphtheroid bacilli found in such large numbers as 2,000 per cubic centimeter (table 3).

questionable. Bile is certainly not an agent likely to interfere with the growth of organisms of the colon-typhoid group. In fact, it is used in special mediums to favor their growth. Furthermore, there is the well known fact that the typhoid bacillus tends to survive in the gallbladder for many years after the original infection and thus to produce carriers. The bactericidal power of the bile for the cocci is questionable. It is easy to find surviving cocci in the bile in experimental animals for long periods after the organisms have been introduced.² This is an observation often recorded. Any one who has tried to preserve pooled specimens of bile or solutions containing bile even when the medium is kept on ice must have noted that organisms of the colon group as well as of the cocci group are present. Magner and Hutcheson³ have reported that certain cocci grow well in the presence of, while others are killed by, bile.

The medium used was probably one of the best for the growth of cocci, having been especially devised for that purpose, and it is difficult

14. Andrews, E.: Unpublished data.

to see how a fraction of a cubic centimeter of bile when diluted in the whole tube could have much inhibitory power.

Numbers of Bacteria Found.—While one cannot, of course, postulate that the number of organisms found in a given location is indicative of the severity of the infection, the general range of findings in our series does seem significant. When one considers the number of bacteria found per cubic centimeter in the best possible milk it seems strange that in a field such as the gallbladder the flora should be so scant in the presence of varying degrees of inflammation as evidenced by microscopic examination. Cultures of the urine of patients with cystitis or of material from the inflamed appendix are of an entirely different grade. Every field in the microscope shows many organisms. Thus we are at a loss to account for the scantiness of the flora found in the gallbladder.

TABLE 7.—Percentage of Gallbladders Showing Infection Classified According to Type of Condition

Type of Condition*	Number of Gallbladders	Wall, Percentage	Fluid Contents, Percentage	50,000+, Percentage
Group 1.....	8	37	12	0
Group 2.....	12	50	33	8
Group 3.....	4	100	100	100
Group 4.....	36	33	25	8
Group 5.....	31	42	42	6

* Group 1 comprised normal gallbladders; group 2, normal gallbladders with stones; group 3, gallbladders from patients with obstruction of the common duct, and groups 4 and 5, gallbladders from patients operated on during the active, and during the quiescent, stage of the disease, respectively.

A striking exception is presented by organisms of the colon group. In most cases in which such organisms were found at all they were present in overwhelming numbers. In the dilutions in which the plates were poured it was possible to estimate the number of bacteria up to 50,000; hence the results of cultures described as "innumerable" represent more than that number per cubic centimeter. It would therefore seem much more rational to attribute a causal significance to the colon bacillus than to the coccus group if any bacterial cause is to be considered.

Bacteria Found in Gallbladders of the Various Groups.—One of the greatest discrepancies encountered is the frequent apparent lack of correlation between the bacteriologic observations and the clinical and pathologic data. Table 7 summarizes the observations on the various groups, but it is obvious from a glance at tables 4 and 5 that there is no significant bacteriologic difference between cultures of material obtained during the active and those of material obtained during the

quiescent stage of the disease. Furthermore, histologically the normal gallbladder either with or without stones contains a flora that seems quite comparable both qualitatively and quantitatively to that of gallbladders removed during either the active or the quiescent stage and in which pathologic changes of various degrees have taken place. Especially striking is the comparison between the latter two groups (group 4 and group 5). While any division of such cases may be somewhat arbitrary and several borderline cases may be put into either group, nevertheless the fact remains that, after due allowance for the human equation is taken into account, the numbers of bacteria found in the two groups were about the same. In group 5 (gallbladders from patients operated on in the quiescent stage) bacteria were found in the wall in 33, and in the fluid contents in 25 per cent, of the specimens, whereas in group 4 (gallbladders from patients operated on in the active stage) 42 per cent yielded positive cultures from the wall, and the figure for the bile was the same. In group 5 as well as in group 2 (normal gallbladders with stones) 8 per cent of the specimens showed high bacterial counts in the bile, while in group 4 only 6 per cent of the gallbladders did. Many specimens in the latter group were from patients operated on during severe attacks of acute cholecystitis, and all were obtained at operations performed within a few days after the colic was over and while the gallbladder still presented definite signs of activity.

Gallbladders Showing Large Numbers of Bacteria.—In ten cases in our series there were overwhelming numbers of bacteria in the counts. In 9 of these the organisms were *Bacillus coli*, and in one, *Streptococcus viridans*. It is interesting to note first that all the gallbladders from patients with high grade obstruction of the common duct yielded rich growths, although the number is too small to mean much. However, one of us ^{7b} noted previously that ligation of the common duct in the dog, although producing but slight pathologic change, almost invariably caused the development of a rich flora in the bile. The element of stasis together with a favorable action of bile on the growth of the colon bacillus is obviously to be considered. One must, however, remember that the mere presence of bacteria does not necessarily mean that inflammation is taking place. It is well known that the most profound stasis resulting from carcinoma of the pancreas typically does not cause inflammation of the gallbladder but that Courvoisier's law postulates that one may expect to find a thin-walled gallbladder in such cases.

Of the ten gallbladders regarded as heavily infected five were from patients with typical cholecystitis, as shown by histologic examination. However, the remaining five showed no microscopic changes or such

slight alterations that they could be considered practically normal if one remembers Graham's statement that the finding of a few wandering cells in the mucosa is normal.⁵ One gallbladder was that of a patient with carcinoma of the pancreas; the gallbladder was not excised, but it appeared normal grossly. Another patient was subjected to cholecystectomy on the evidence of a stone in the gallbladder, but the patient had course showed that the diagnosis was wrong and that the patient had an abscessed appendix and a suppurative portal thrombophlebitis. The specimen from that patient was unfortunately lost. The other three gallbladders exhibited but minimal change.

It appears, then, that the finding of enormous numbers of bacteria does not necessarily indicate a severe clinical picture, as only half of the gallbladders showed true pathologic changes.

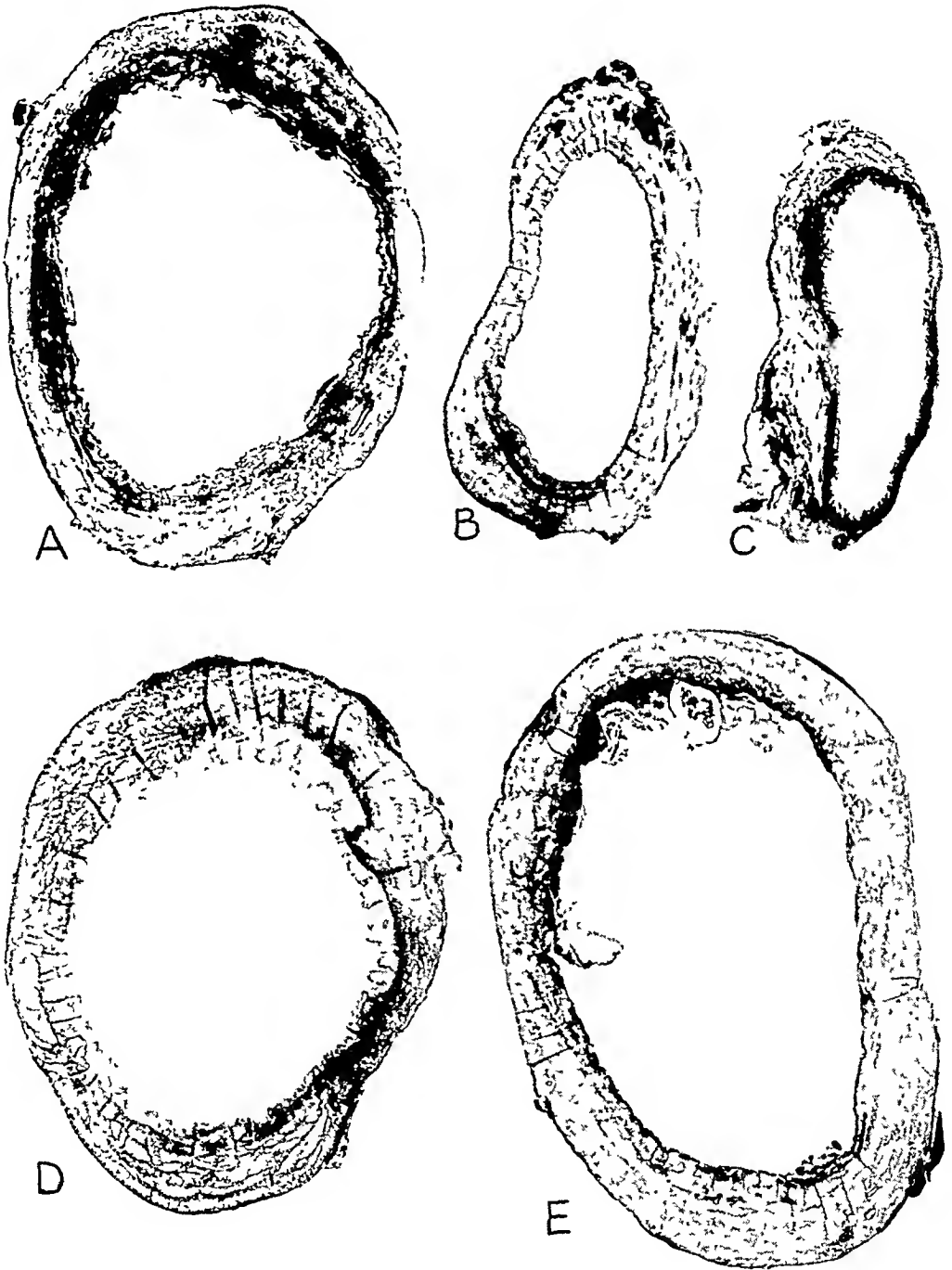
Definitely Damaged Gallbladders with Sterile Contents.—There were sixteen severely damaged gallbladders, all of which for obvious clinical reasons were classified as belonging to group 4. All the patients from whom these specimens were obtained had or had had acute symptoms referable to the gallbladder within a few days before the operation. All the cultures, i. e., from both the wall and the contents, were sterile. In this as in the last group glaring inconsistencies cause one to pause. Six of the specimens showed relatively slight damage to the wall. This is an illustration of the remarkably quick reparative power of the gallbladder, which had been commented on by Boyd.¹⁵ All the other specimens on microscopic examination were found to show changes typical of those of moderate or severe cholecystitis with high grades of pathologic changes in the acute stage. The figure shows photomicrographs of some of these specimens and illustrates the advanced stage of pathologic degeneration encountered. Again one is at a loss to explain the gross lack of correlation between the bacteriologic and the histologic picture and to fit the two together on the assumption that cholecystitis is a disease of purely bacterial origin.

SUMMARY OF OBSERVATIONS

The normal human gallbladder, the undamaged stone-containing gallbladder and the pathologically damaged gallbladder as removed either in the active or in the quiescent stage of the disease contain bacteria in a minority of cases.

The differences between the various flora of different types of gallbladders fall within the limits of chance variation, both qualitatively and quantitatively.

15. Boyd, W.: Surgical Pathology, Philadelphia, W. B. Saunders Company, 1925.



Severe pathologic changes in five gallbladders the walls and fluid contents of which were sterile. Note the extensive thickening and infiltration. Note the marked asymmetry of damage in C.

Gallbladders removed during the most acutely active stage of the disease did not yield an appreciably richer flora than other types. Gallbladders in which a rich flora was found showed no more extensive pathologic changes than did the average specimens in the series.

Conversely, in gallbladders in which extensive histologic evidence of damage was present the flora was no richer than in the average specimen.

An actual majority of the most severely damaged gallbladders were sterile.

The colon bacillus was the only organism that occurred in large numbers. With a single exception the cocci were few in bacterial counts.

COMMENT

The results of our studies as summarized can be interpreted in four different ways, namely: 1. Our cultural methods are at fault. 2. The disease is caused by some unknown organism or virus. 3. The organisms present have been killed by "stewing" in their own juice. 4. Bacteria play but a minor or secondary rôle in disease of the gallbladder.

1. *Faulty Cultural Methods.*—This possibility has been discussed earlier in the paper, and we believe that the answer is "no." Our results are quite in accord with nearly all previous results as to the number of specimens which proved sterile. Even the most enthusiastic advocates of any particular organism as the etiologic agent have uniformly failed to find that organism in more than a minority of cases. Beginning with investigations made by Welch, who found *Bacillus Welchii* occasionally in bile, many such studies have been made by competent bacteriologists in many countries, and the results have been uniformly of the same order as ours, although there has been some variation in detail. In all investigations the same general flora was found and the incidence of the organisms was within the same range; also half or two thirds of the cultures yielded no bacteria at all. The overwhelming literature in this field cannot be reviewed here, but summarizing articles by Magner and Hutcheson³ in English and by Seeber¹⁶ and Löwenberg and Meyer¹⁷ in German may be referred to (table 8). One hesitates to accuse a whole generation of bacteriologists of incompetence.

16. Seeber, F.: *Klinische und bakteriologische Untersuchungen bei Erkrankungen der Gallenwege*, Deutsches Arch. f. klin. Med. **167**:186, 1930.

17. Löwenberg, W., and Meyer, W.: *Enterococcus Infections of the Gallbladder*, Elective Localization of Pathogenic Microbes, Klin. Wchnschr. **5**:989, 1926.

2. *Unknown Organism or Virus as Cause of the Disease.*—While this, of course, cannot be denied categorically, the hypothesis is not in accord with the usual expectation in cases of abdominal inflammation. Lesions of the colon, appendix, urinary bladder, pancreas, kidney and female genitalia are all caused by combinations of mechanical or vascular insults, often complicated by infection, or by infection alone. In all cases the known bacterial flora has proved ample to explain the conditions found.

TABLE 8.—*Cultures from Gallbladders* ³

	Number	Positive, per Cent	Strepto- cocci, per Cent	B. Coli, per Cent	Staph- ylococci, per Cent	B. Welchii, per Cent	Other Bacteria, per Cent
1932, Authors, present series							
Fluid contents.....	106	33	6.5	17.9	4.7	5.6
Wall.....	200	89	29.5	26	26	1	18
1928, Wilkie							
Fluid contents.....	50	12	4	6	2
Wall.....	50	12	4	6	2
1930, Gordon-Taylor and Whitby							
Fluid contents.....	50	32	8	12	6	6
Wall.....	50	82	22	18	16	26
1929, Branch							
Fluid contents.....	210	40	15	50	18	5	9
Wall.....	210	53	11	49	17	8	10
1928, Friesleben							
Fluid contents.....	132	47	11	28	8
Wall.....	96	76	13.5	28	32	2
1927, Illingsworth							
Fluid contents.....	100	40	17	21	3
Wall.....	100	62	39	22	6
1927, Judd, Mentzer and Parkhill							
Fluid contents.....	193	14.5	8	6	1	0.5	4
Wall.....	200	49	18	4.5	10	1	20
1916, Rosenow							
Fluid contents.....	29	55	17	31	24
Wall.....	32	84	56	28	22	22
1925, Johnson							
Fluid contents.....	100	32	3	18	7	4
1924, Blalock							
Fluid contents.....	270	58	5	31	10.7
1922, Drennan							
Fluid contents.....	100	19	2	12	4	1
Average of results							
Fluid contents.....	1,340	34.7	8.7	21			
Wall.....	938	63.4	24	22.6			

3. *Destruction of Organisms "Steeping" in Their Own Juice.*—It is well known that in many cases of acute infection there are stages of the disease in which the in vitro cultivation of bacteria is impossible. The finding of sterile pus is not surprising to any surgeon or bacteriologist even in cases in which smears show many bacteria. Classic examples of this are empyema of the chest and tubo-ovarian and appendical abscess. There are, however, marked objections to this hypothesis. First, the gallbladder, even the acutely diseased one, has been found sterile by all students in a proportion of cases far higher

than that obtaining for other inflamed viscera. While sterile pus is not a rarity in other diseases, it is decidedly exceptional, and one would not expect to find it in an actual majority of cases. We feel sure that any surgeon who was told by his laboratory staff that pus was sterile in two thirds of his cases would soon start an investigation as to the competence of that staff. Second, the presence of sterile pus is a definite stage in many diseases. It occurs after the acute infection is over, the host has built up antibodies and time has elapsed for the development of enough growth products to kill the bacteria. In disease of the gallbladder the observations are quite different. Bacteria are present or absent in about equal numbers at all stages of the process, which is quite a different matter from the nontuberculous "cold abscess" and is not in any way comparable to it.

4. *Minor or Secondary Rôle Played by Bacteria in Disease of the Gallbladder.*—Before the rôle of bacteria can be adequately considered, one must examine the question of whether or not there is a normal flora of the gallbladder. Our own cultures of normal gallbladders, of normal gallbladders containing stones as well as of specimens obtained during the quiescent stage of the disease indicate that there is such a flora and that it is comparable in degree and kind with that found in actively diseased gallbladders.

The presence of bacteria in normal gallbladders is not by any means a new observation. Osler⁴ noted the fact that in cases of typhoid fever large numbers of typhoid bacilli were almost uniformly found in the bile, in spite of the fact that cholecystitis was a comparatively rare complication, having been found by him in only 19 of 1,500 cases of typhoid fever. Furthermore, it is well known that in cases of bacteremia from many causes, although many organisms find their way into the bile, the occurrence of cholecystitis is rare. Cultures of human bile taken post mortem have long been known to be positive, but this observation has generally been ignored as it was thought that agonal or postmortem changes were a sufficient explanation. However, there has been a gradual accumulation of other facts that seem to lead to a different interpretation. It has been observed in experimental animals that the gallbladder contains bacteria in a high percentage of cases. Walsh and Ivy¹⁸ found this quite uniformly. One of us^{7b} made similar observations, although he found dogs' bile to be sterile in most cases while the wall of the gallbladder contained bacteria, and Ivy found bacteria in the bile itself frequently. Probably the general con-

18. Walsh, E. L., and Ivy, A. C.: The Etiology of Gallstones, *Ann. Int. Med.* 4:134, 1930.

dition of the animals, as well as the diet and the temperature of the cages, has considerable influence. Recent work by Graham has shown the intimate association between the lymphatics of the gallbladder and those that drain the bowel, and besides it has long been known that the liver receives some of the portal lymph drainage through this network. Zinsser¹⁹ noted that a considerable range of intestinal flora is carried to the liver and destroyed. In his book on infection and immunity he called attention to the fact that bacteria frequently lie dormant in the tissues and cause no infection unless other damage to the tissue is produced. He quoted the experiments of Tarozzi, who injected tetanus spores into the portal circulation. These were carried to the liver and lay dormant for as long as fifty days. Trauma of animals into whose circulation tetanus spores had been injected caused tetanus.

The experiments of Arnold²⁰ are pertinent. He showed that during certain stages of normal digestion in the dog the permeability of the duodenum is so great that as many as 1,000 bacteria per cubic centimeter can be plated from a cervical lymphatic fistula. Normally, of course, these are destroyed by elements of the reticulo-endothelial system, especially by the Kupffer cells of the liver. Ellis and Dragstedt⁶ found that a spore-forming anaerobe is a constant inhabitant of the livers of dogs. Andrews and Hrdina^{7a} showed that this is a true Welch bacillus and found that it can be isolated from dogs' muscle as well. In their animals it was present in small numbers and generally was not recovered in cultures made by simply swabbing the cut surface. On the other hand, if the material was first incubated for twenty-four hours, the foul odor and rapid formation of explosive gas in cultures failed only once in over one hundred experiments. Experiments⁸ in which a dog's leg was ligated tightly with wire showed that not only gangrene but actually gas gangrene occurred as a rule. Blood-borne or exogenous infection seems to be ruled out. The identification of this organism by Wolbach and Saiki²¹ was first made in 1909 and has been confirmed in many laboratories. Recent denial of its identity with the true Welch bacillus on immunologic grounds by Trusler and Reeves²² does not conform to the usual accepted bacteriologic standards.

19. Zinsser, Hans: *Infection and Resistance*, New York, The Macmillan Company, 1923.

20. Arnold, L.: *Alterations in the Endogenous Bacterial Flora and Microbic Permeability of the Intestinal Wall*, *J. Hyg.* **29**:82, 1930.

21. Wolbach, S. B., and Saiki, T.: *A New Anaerobic Spore Bearing Bacterium Commonly Present in the Livers of Healthy Dogs*, *J. M. Research* **21**:267, 1909.

22. Trusler, H. M., and Reeves, J. B.: *The Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis*, *Arch. Surg.* **28**:479 (March) 1934.

As shown by Judd and his associates,²³ its pathogenicity is low, and our own experience has been that not only anaerobes but a large section of the usual intestinal flora are present. The anaerobes have received more prominence because they are hardier, spore-forming bacteria while the others are easily killed (David and Loring²⁴). Human livers examined at autopsy showed the same flora as that present in the livers of dogs. The usual question as to whether the flora found at autopsy is an agonal one is hard to answer. In order to rule out this factor we have been trying to obtain livers from patients who died suddenly. Thus far seven specimens have been examined, all of which yielded positive cultures.

The mere presence of the gallbladder in such a field suggests that it would be unusual in the highest degree if it did not occasionally share the flora of the adjacent liver. How many of the organisms pass into its lumen or enter it through the cystic duct is problematic, but that a few may frequently do so has been the universal experience of chemists who have tried to study bile. Bile affords such an ideal culture ground for many types of bacteria that chemical studies of pooled bile have always been handicapped by the fact that it is practically impossible to secure sterile specimens of bile either from man or from animals. Even bile withdrawn under the most careful aseptic precautions rapidly undergoes bacterial decomposition and must be sterilized by heat or addition of alcohol. This fact, quite familiar to all who have worked in this line, is indicative of a normal biliary flora.

The association of disease of the gallbladder with infection has in many ways been a rather forced one. The experimental production of cholecystitis by many types of virulently pathogenic organisms is no proof whatever that this process goes on in man. It is obvious that members of the coccus group or the colon bacillus group incite supuration wherever placed in the body. When one considers that organisms injected intravenously tend to lodge in the liver and hence get into the bile naturally, it is obvious that some reaction may take place. Nevertheless, acute cholecystitis as it occurs in man has never been produced in that manner. The enormous thickening and induration of the wall, the swelling with closure of the cystic duct and the general picture surgeons know so well is not reproduced. All that can be found even after injections of overwhelming numbers of organisms is a slight to moderate cellular infiltration of the walls. On the other hand, Peter-

23. Thorsness, E. T.: *Bacteriology of Cholecystitis*, Surg., Gynec. & Obst. 59:752, 1934.

24. David, V. C., and Loring, M.: *The Rôle of the Welch Bacillus in Experimental Peritonitis*, Arch. Surg. 26:1103 (June) 1933.

man and Graham,²⁵ Cushing,²⁶ Meyer and his co-workers²⁷ and many others have pointed out that in order to produce experimental cholecystitis with any regularity it is necessary to damage the viscus or interfere with its blood supply. Especially striking are the results of Peterman and Graham,²⁵ who injected large numbers of virulent colon bacilli into the gallbladder through the cystic duct with no resulting infection. Equally striking is the fact that just as typical inflammatory reactions may be produced by means other than bacteria. Ivy noted the great susceptibility of the dog's gallbladder to infection after trauma. One of us^{7b} produced typical changes both histologically and bacteriologically by ligating the cystic duct. The mere insertion of a needle into the gallbladder of a dog frequently stirs up an inflammatory reaction quite as typical as that produced by bacteria.

Furthermore, histologic investigation²⁸ of diseased gallbladders does not lend support to the infective theory. This point has been emphasized recently by Feinblatt.²⁹ His studies gave the same results as our own. The chief factors in the pathologic picture are edema, hemorrhage and infiltration by round cells. Pus cells are few, even in many acute cases. These points seem to fit better with mechanical or vascular insults than with infection alone. Feinblatt examined smears from twenty gallbladders with empyema and found that the material which resembled pus contained few leukocytes. In the majority of the cases the material was sterile on culture. Our own observations indicate that there is no increase in the number of leukocytes present in bile from diseased gallbladders.²⁹

Seeber's¹⁶ results are even more striking. In the series reported by him about half of the gallbladders were sterile. Those from febrile patients showed *B. coli* in about twice the number that those from afebrile ones did. Nevertheless one fourth of the gallbladders from febrile patients were sterile.

Since the results of our studies tend to minimize the importance of bacteria, one must search for other causes. Some progress has already been made along this line. An example of pancreatic apoplexy which we observed causes one to suspect the entrance of chemically

25. Peterman and Graham, cited by Graham.¹³

26. Cushing, H., quoted by Meyer et al.²⁷

27. Meyer, K. F.; Nelson, N. M., and Fensier, M. L.: Mechanism of Gallbladder Infection in the Laboratory Animals, *J. Infect. Dis.* **28**:456, 1921.

28. Andrews, E.: Detailed Studies of a Series of Gall-Bladder Cases, *Surg., Gynec. & Obst.* **57**:23, 1933.

29. Feinblatt, H. M.: The Infrequency of Primary Infection in Gall-Bladder Disease, *New England J. Med.* **199**:1073, 1928.

toxic material in a retrograde manner. Wolfer³⁰ has shown that pancreatic juice sets up a moderate degree of inflammation in the gallbladder. This observation has been confirmed by Andrews, Goff and Hrdina.³¹ Gastric juice is even more toxic than pancreatic juice, and intestinal contents are of about the same grade of toxicity (Andrews). Even more striking is the proof by Mann³² that chemicals may be excreted in such amounts in the bile that typical inflammatory changes are produced in the gallbladder. Chlorine administered intravenously which the most prominent pathologic feature is edema characteristic of human acute cholecystitis (figure). Furthermore, Copher, Glover and Kendall³³ have also produced cholecystitis by the intravenous injection of material derived from obstructed loops of intestine. Again edema was marked.

A recent suggestion by one of us may be added. In line with the view that gastric ulcer is undoubtedly caused by the corrosive power of the acid juice, one cannot afford to overlook the possibility that a similar mechanism may be at work in the gallbladder. Demonstrations by Dragstedt, Mann and others that pure gastric juice has the power to produce ulcers with great regularity in isolated segments of the stomach make one wonder why equal consideration cannot be given to the bile. It contains a substance, bile salts, the toxicity of which is quite comparable to that of hydrochloric acid. These salts are concentrated in the gallbladder to the enormous degree that they may reach 10 per cent strength (Hammarsten³⁴), although most of our own observations fall short of this figure. Solutions of this strength have been shown by Rewbridge and Hrdina³⁵ to be capable of causing fatal peritonitis, myositis or pneumonitis. Pancreatitis with fat necrosis was also observed by Rewbridge.³⁶ Thus there may occur the apparently

30. Wolfer, J. A.: *Rôle of Pancreatic Juice in the Production of Gallbladder Disease*, Surg., Gynec. & Obst. **53**:433, 1931.

31. Andrews, E.; Goff, M., and Hrdina, L.: *Effect of Pancreatic Juice on the Absorptive Mechanism of the Gall-Bladder*, Proc. Soc. Exper. Biol. & Med. **29**: 1091, 1932.

32. Mann, F. C.: *Production by Chemical Means of a Specific Cholecystitis*, Ann. Surg. **73**:54, 1921.

33. Copher, Glover H., and Kendall, quoted by Graham,¹³ Wiley & Sons, Inc., 1911.

34. Hammarsten, O.: *Textbook of Physiological Chemistry*, New York, John Wiley & Sons, Inc., 1911.

35. Rewbridge, A. G., and Hrdina, L.: *Etiological Rôle of Bacteria in Bile Peritonitis*, Proc. Soc. Exper. Biol. & Med. **27**:528, 1930.

36. Rewbridge, A. G.: *Fat Necrosis in Bile Peritonitis*, Arch. Path. **12**:70 (July) 1931.

paradoxical train of events that too strong a concentration of the solvent (bile salts) provokes an inflammation capable of producing absorption and hence precipitation of the cholesterol held in solution by them.

CONCLUSION

The results of our studies suggest that bacteria may play but a secondary rôle in disease of the gallbladder and that other possible factors, mechanical, vascular, toxic and chemical, deserve more careful study.

PATHOLOGY OF THE VESSELS OF THE PULMONARY CIRCULATION

PART V

O. BRENNER, M.D., M.R.C.P.
Physician for Outpatients and, Physician in Charge of the Cardiographic
Department, Queen's Hospital
BIRMINGHAM, ENGLAND

TUBERCULOSIS OF THE PULMONARY VESSELS

Tuberculosis of the pulmonary vessels is probably always present in cases of plithisis. The process affects successively the adventitia, media and intima of vessels in the walls of tuberculous cavities. The wall of the vessel may bulge, giving rise to the aneurysms of Rasmussen, which may burst and cause severe hemoptysis. Usually this is prevented by the occurrence of thrombosis. The erosion of a caseous gland into a pulmonary vein and the discharge of its contents into the lumen constitute a well known cause of miliary tuberculosis. Occasionally, isolated tuberculous vegetations occur in the intima of large pulmonary arteries and veins.*

In the present series pulmonary tuberculosis was present in 6 patients and all showed tuberculosis of the pulmonary vessels. Arteries and veins of all sizes were affected, but involvement of the small vessels was commonest.

1. LARGE ELASTIC ARTERIES

In a woman of 65 with chronic, relatively inactive fibrocaseous tuberculosis with cavitation of the upper lobe of the right lung, an artery 2.2 mm. in diameter was involved. Its intima was normal. The whole thickness of the media in two long stretches was completely necrotic. The adventitia adjacent to these areas showed rather inactive tuberculosis, with much fibrosis and some caseation and calcification. This was continuous with a large fibrocaseous patch in the adjacent lung tissue. It is noteworthy that although the caseous process was separated from the lumen of the artery only by the internal elastic lamina and a layer of endothelium, there was no overlying thrombosis. A slight extension of the lesion would have caused the artery to burst.

In this case several small veins also were involved.

In this series of five papers the superior numbers refer to the bibliography which is printed at the end of this paper. The superior letters refer to footnotes.
(r) 122, 138.

paradoxical train of events that too strong a concentration of the solvent (bile salts) provokes an inflammation capable of producing absorption and hence precipitation of the cholesterol held in solution by them.

CONCLUSION

The results of our studies suggest that bacteria may play but a secondary rôle in disease of the gallbladder and that other possible factors, mechanical, vascular, toxic and chemical, deserve more careful study.

PATHOLOGY OF THE VESSELS OF THE PULMONARY CIRCULATION

PART V

O. BRENNER, M.D., M.R.C.P.

Physician for Outpatients and, Physician in Charge of the Cardiographic
Department, Queen's Hospital
BIRMINGHAM, ENGLAND

TUBERCULOSIS OF THE PULMONARY VESSELS

Tuberculosis of the pulmonary vessels is probably always present in cases of phthisis. The process affects successively the adventitia, media and intima of vessels in the walls of tuberculous cavities. The wall of the vessel may bulge, giving rise to the aneurysms of Rasmussen, which may burst and cause severe hemoptysis. Usually this is prevented by the occurrence of thrombosis. The erosion of a caseous gland into a pulmonary vein and the discharge of its contents into the lumen constitute a well known cause of miliary tuberculosis. Occasionally, isolated tuberculous vegetations occur in the intima of large pulmonary arteries and veins.^x

In the present series pulmonary tuberculosis was present in 6 patients and all showed tuberculosis of the pulmonary vessels. Arteries and veins of all sizes were affected, but involvement of the small vessels was commonest.

1. LARGE ELASTIC ARTERIES

In a woman of 65 with chronic, relatively inactive fibrocaseous tuberculosis with cavitation of the upper lobe of the right lung, an artery 2.2 mm. in diameter was involved. Its intima was normal. The whole thickness of the media in two long stretches was completely necrotic. The adventitia adjacent to these areas showed rather inactive tuberculosis, with much fibrosis and some caseation and calcification. This was continuous with a large fibrocaseous patch in the adjacent lung tissue. It is noteworthy that although the caseous process was separated from the lumen of the artery only by the internal elastic lamina and a layer of endothelium, there was no overlying thrombosis. A slight extension of the lesion would have caused the artery to burst.

In this case several small veins also were involved.

In this series of five papers the superior numbers refer to the bibliography which is printed at the end of this paper. The superior letters refer to footnotes.
(x) 122, 138.

2. SMALL MUSCULAR ARTERIES

The small muscular arteries were involved in 5 cases. The affected vessels were always near tuberculous foci in the lungs. The commonest lesion was endarteritis obliterans. The lumen was greatly narrowed or completely obliterated by loose fibrillar connective tissue containing many lymphocytes, large mononuclears and occasionally tuberculous giant cells. Capillary lumens also were often present. In a case in which there were dense old scars at the apexes of the lungs the small arteries in the scars showed an intima consisting of thick, dense connective tissue greatly narrowing or obliterating the lumen, apart from a few recanalizing lumens. The media in some of these arteries was replaced by dense hyaline connective tissue over long stretches. In the other cases it was occasionally normal but usually showed infiltration with cells similar to those in the intima, and often on the side next to the tuberculous focus in the lungs it showed caseation with complete loss of structure. Sometimes when an artery was traced into a tuberculous focus in the lung and before the caseous mass was reached, the lumen was occluded by tuberculous granulation tissue, while the media was still normal. When the caseous mass was reached the internal and external elastic laminae frayed out and disappeared, and finally the artery was lost as it merged with the caseous mass. Changes such as these were observed in only a few arteries in each of the 5 cases. They were never widespread enough to cause obstruction to the pulmonary circulation.

3. SMALL VEINS

The small veins were involved in 3 cases. In all of them the intima showed thickening by loose fibrillar connective tissue containing many lymphocytes, large mononuclears and polymorphonuclears and occasionally a few capillary lumens. Usually there was a similar process in the media and adventitia, the whole thick wall of the vein then consisting of loose cellular, vascular connective tissue. Sometimes the portion of the wall adjacent to the tuberculous focus in the lung was caseous.

4. LARGE INTRAPULMONARY VEINS

The large intrapulmonary veins were involved in only 1 case. The intima of veins near tuberculous foci showed patchy thickening by loose cellular connective tissue containing capillary lumens. The media showed a similar but less extensive process. The adventitia consisted of dense vascular connective tissue showing some infiltration with lymphocytes and large mononuclears.

RHEUMATISM OF THE PULMONARY ARTERIES

Attention has recently been drawn to the widespread lesions in blood vessels occurring in the course of acute rheumatism. Little clinical

importance has been attached to these, though Swift²⁹³ attributed the common cardiac pain in cases of rheumatic disease to involvement of the arteries, particularly the aorta; Slater²⁸⁰ reported 3 cases of occlusion of the coronary artery in the course of rheumatic fever, and Neale²¹⁸ described 2 cases of rupture of the aorta in the course of acute rheumatism. Two cases of rheumatism of the pulmonary arteries were observed in the present series.

CASE 1.—H. C., a man aged 39, died of congestive heart failure due to rheumatic cardiac disease with mitral stenosis and auricular fibrillation. At autopsy the usual signs of chronic venous congestion were observed. The heart weighed 525 Gm. All the chambers were dilated, and the left auricle and right ventricle were hypertrophied. The mitral valve showed extreme stenosis, and there were slight old changes in the aortic valve also. In addition there were recent vegetations on the mitral, aortic and pulmonary cusps. The pulmonary arteries were somewhat dilated and showed marked atherosclerosis. An adherent thrombus was present in the main branches to the right lower and middle lobes. Microscopically the stem of the pulmonary artery showed moderate atherosclerosis. The main branches to the right and left lungs (fig. 31) showed a great deal of atherosclerosis, the intima being 0.83 mm. thick, compared with a thickness of from 0.25 to 0.33 mm. for the media. The adventitia consisted of dense fibrous tissue. Many of the vasa vasorum were almost occluded by cellular intimal thickening, and around them was much infiltration with large mononuclears, lymphocytes and fibroblasts. The media in several long stretches showed ingrowth from the adventitia of many capillaries, young connective tissue and many round cells. There the elastic laminae and muscle were interrupted and destroyed, sometimes in the whole thickness of the media. In other areas the portion of the media immediately beneath the intima was swollen and degenerate, consisting of fibrous tissue with a few shrunken muscle cells and a few short irregular elastic fibers. The intima consisted of dense fibrous tissue with a little calcification near the surface. There were many spindle cells and small groups of fat-containing foam cells. Over the damaged part of the media the round cell infiltration spread into the deeper parts of the intima. No other rheumatic changes were observed in the lungs or in the vessels of any other organ.

CASE 2.—I. B., a woman aged 26, died of congestive heart failure due to rheumatic cardiac disease with mitral stenosis and incompetence. At autopsy the usual signs of chronic venous congestion were observed. The heart weighed 750 Gm. The pericardium was universally adherent to the surface of the heart. There were great dilatation of all the cavities and hypertrophy of both ventricles, especially the right. The mitral cusps showed great old sclerosis with shortening and thickening of the chordae tendineae, but the fibrous ring surrounding the valve was dilated. There was slight old sclerosis of the aortic and tricuspid cusps. Recent vegetations were present on the mitral, tricuspid and pulmonary cusps. The pulmonary arteries were dilated and showed marked atherosclerosis. Microscopically the stem and large intrapulmonary branches (fig. 32) showed fairly marked atheroma. Many of the large branches (fig. 32) also showed large or small patches of endothelial hyperplasia, forming large polypoid masses of large oval or spindle-shaped cells with vesicular nuclei, projecting into the lumen. A few red blood cells and many large mononuclears and lymphocytes and a few polymorphonuclears were entangled in the mass, and the underlying intima often showed infiltration with similar cells. The media and

adventitia were normal apart from intimal thickening of some of the vasa vasorum. The largest endothelial mass seen, in an artery 1.1 mm. in external diameter (lumen, 0.7 mm.), was 1.7 mm. in diameter at its base and projected for 0.4 mm. into the lumen. The main veins in this case also showed infiltration with lymphocytes and large mononuclears in all three coats. This was also possibly a rheumatic change.

LARGE ARTERIES

Changes in large arteries are probably common. Kugel¹⁵² noted gross changes in 2 of 24 cases of acute rheumatic carditis and microscopic

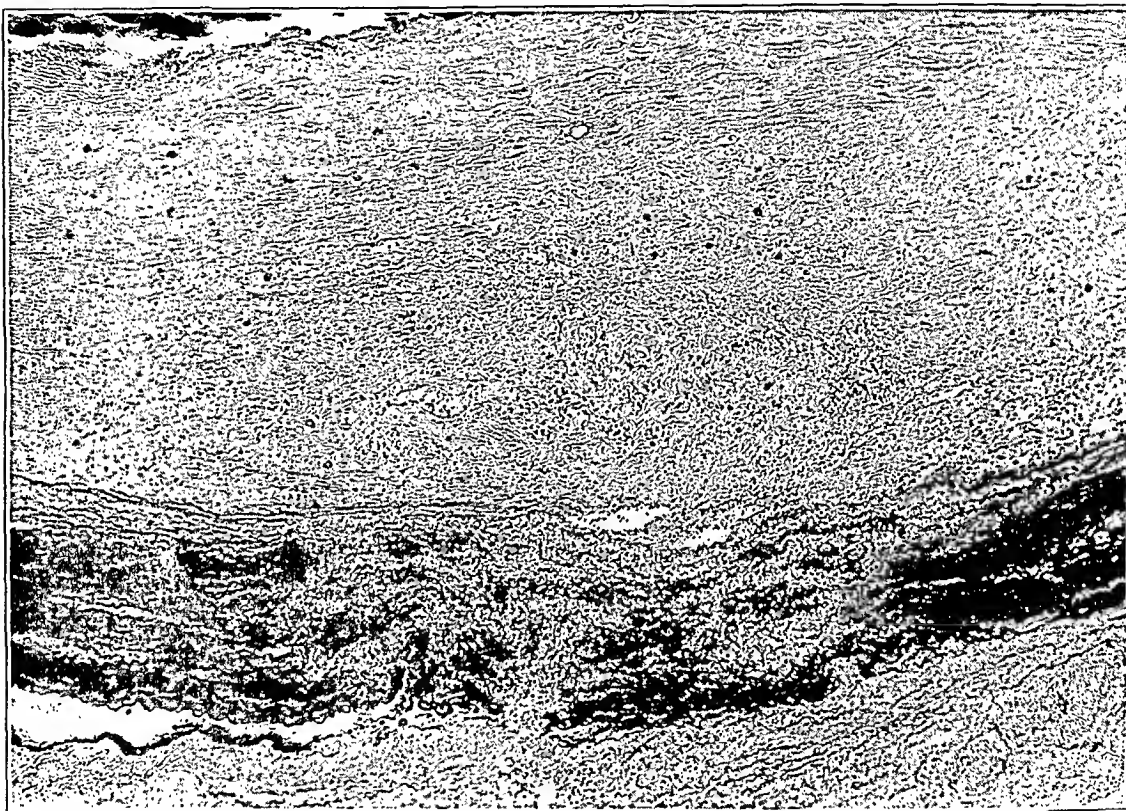


Fig. 31.—Photomicrograph of a section of a pulmonary artery to the right lung showing rheumatic arteritis ($\times 84$; stained with Verhoeff's elastic tissue stain and Van Gieson's stain). There is invasion of the media by new vessels, young connective tissue and many round cells and disruption of the elastic laminae. Great intimal thickening is seen with some round cell infiltration.

changes in 17. In the acute stage the lesions appeared as small, irregular grayish-yellow or brown patches, different from the surrounding atherosclerotic plaques.^y In the chronic stage there was a rippling or pitting of the intima^z with thinning of the underlying media. Gray¹²⁰ observed a dissecting aneurysm of the pulmonary artery in

(y) 152, 222.

(z) 55, 120.

1 of his cases, and Neale ²¹⁸ described 2 cases of rupture of the aorta. Microscopically, sometimes Aschoff nodules were seen in the adventitia,^a but more usually there was a fairly diffuse round cell infiltration of the adventitia, often most marked around the vasa, which frequently showed endarteritis obliterans. The infiltration, as in case 1, spread into the media, destroying the elastic laminae and muscle. The intima sometimes escaped but often showed round cell infiltration, at times surrounding areas of collagenous necrosis. Pappenheimer ²²² described this type of

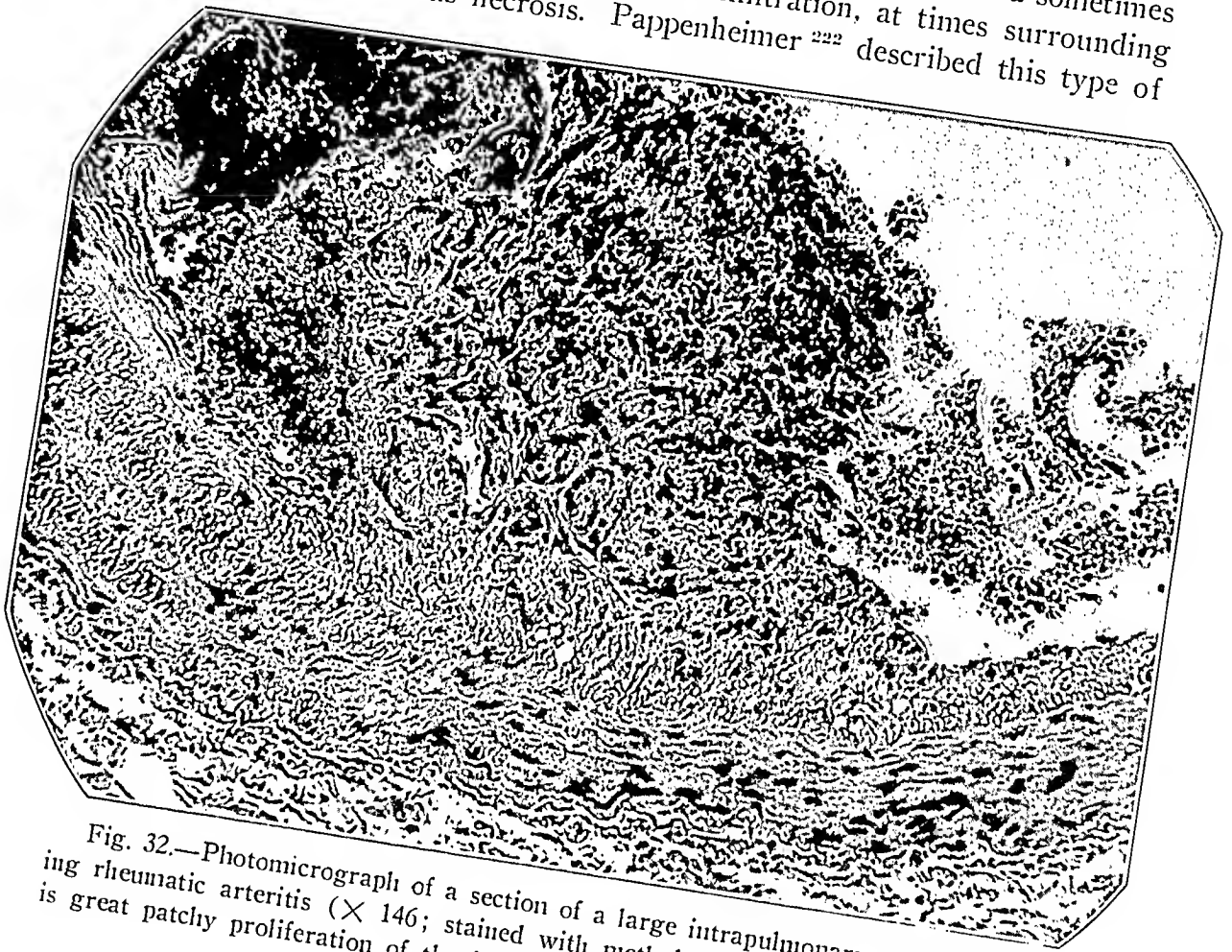


Fig. 32.—Photomicrograph of a section of a large intrapulmonary artery showing rheumatic arteritis ($\times 146$; stained with methylene blue and eosin). There is great patchy proliferation of the intimal endothelium.

lesion as the result of invasion from the lumen of the artery rather than of spread from the adventitia.

In the healed stage there were perivascular fibrous scars in the media, or sometimes large scarred areas interrupting the elastic laminae.

The lesions were strikingly similar to those seen in cases of syphilitic mesarteritis, and, notwithstanding the statement of Pappenheimer ²²² to the contrary, the cellular infiltration and destruction of medial elastic tissue sometimes were as great as in that condition. Caussade ⁵³ described the case of a patient with mitral stenosis with a negative Wassermann

(a) 152, 222, 229, 230.

reaction in whom such lesions were observed as a case of "arterite syphilitique pulmonaire chez un cardiaque noir," and perhaps similar mistakes are commonly made. There are three chief differences between rheumatic and syphilitic arteritis: 1. Many of the cells are large with one or occasionally more nuclei, though as in cases of syphilis there may also be many lymphocytes and plasma cells. 2. The lesion commonly extends to the intima. In cases of syphilis the only change in the intima is a reactive acellular fibrosis. 3. Aschoff nodules or great endothelial proliferation of the intima of the vasa vasorum in the adventitia are sometimes observed in cases of rheumatic disease.

In view of the frequency and severity of the lesions, it is remarkable that serious consequences do not frequently follow, though 1 case of dissecting aneurysm of the pulmonary artery¹²⁰ and 2 cases of rupture of the aorta²¹⁸ in which similar lesions occurred have been described. True rheumatic aneurysms are exceedingly rare, though the dynamic dilatation of the aorta and pulmonary artery seen in the roentgenograms in cases of rheumatic cardiac disease have been attributed to these changes.⁵⁵

MEDIUM-SIZED ARTERIES

In arteries from 1 to 10 mm. in diameter Gouley¹¹⁹ described endothelial proliferation which almost occluded the lumen and which was similar to that in case 2. In somewhat larger vessels in addition to this there sometimes were lesions in the media similar to those in the large arteries. That is almost the only reference to rheumatic lesions in medium-sized pulmonary arteries, though Pappenheimer²²² said that in systemic arteries of that size there may be cellular infiltration of the intima, sometimes with polymorphonuclear infiltration of the media.

SMALL ARTERIES

Small arteries are said to be involved in from 20 to 40 per cent of cases of acute rheumatism.²²⁹ Similar changes also occur in the small systemic arteries.²²⁴ The wall of the vessel is necrotic, and it and the surrounding tissues are infiltrated with fibrin and surrounded by an infiltration of polymorphonuclears, large mononuclears, lymphocytes and plasma cells. There may be extravasation of blood into the wall of the vessel. When healing occurs, new capillaries grow in from the adventitia, and the lumen becomes greatly narrowed by the development inside the elastica interna of a thick layer of loose cellular vascular connective tissue resembling an organized thrombus. Brenner⁴³ described a case of mitral stenosis in which many of the small pulmonary arteries showed great intimal thickening by cellular connective tissue, often with reduplication of the elastica interna, but he concluded that the endarteritis obliterans was probably a reaction to the chronic (possibly rheumatic)

pneumonic process in the lung tissue and was not due directly to rheumatism. It is possible that such lesions, if widespread, may help to embarrass further an already damaged heart.

CAPILLARIES AND VENULES

The capillaries and venules were sometimes involved in the necrotic process described by Pappenheimer²²² and ruptured readily. That may be the cause of the early hemoptysis noted in cases of rheumatic cardiac disease.

SEPTIC INFLAMMATION OF THE PULMONARY VESSELS

Acute and subacute infections of the pulmonary arteries and veins are common but are usually merely incidents in an infective illness that is fatal in itself. The cases may be classified according to the manner in which the infection reaches the pulmonary vessels:

MODE OF INVASION

I. *Spread by Continuity from Infective Endocarditis of the Pulmonary Valve.*—No examples of this were found in the present series, but it has been described in cases of pulmonary infective endocarditis due to the gonococcus, pneumococcus or influenza bacillus.^b The ulceration spreads from the cusps of the valve for a variable distance up the pulmonary artery. Microscopically the intima is seen to be replaced by fibrin and leukocytes, and there is polymorphonuclear infiltration of the underlying media, with areas of partial repair, as shown by the presence of cellular vascular scars.

II. *Invasion from Without by Direct Spread from an Infective Process in the Surrounding Tissues.*—This is much commoner and occurred in 4 cases in the present series. In 2 there was a chronic pulmonary abscess and in the others chronic pneumonia, associated in 1 case with bronchiectasis. Several vessels were involved in each case. In 2 the small arteries and in 3 the small veins were affected.

A. *Arteries:* In 1 case many small arteries showed a thick intima consisting of loose connective tissue infiltrated with lymphocytes and polymorphonuclears. There was slighter cellular infiltration of the media and adventitia. In the other case there was dense lymphoid infiltration of the adventitia, penetrating into the media but not into the intima. In each case all the affected vessels were either near a large chronic pulmonary abscess or in areas of chronic pneumonia surrounding bronchiectatic cavities.

B. *Veins:* The affected veins had an external diameter of from 0.4 to 0.5 mm. and were always in chronic pneumonic areas or near

(b) 201, 294.

the wall of a chronic pulmonary abscess. In 1 case small bronchial veins were similarly affected. The intima was considerably thickened. It consisted of loose connective tissue, sometimes with a number of capillary lumens, and contained many lymphocytes and sometimes large mononuclears and polymorphonuclears. The media and adventitia showed similar round cell infiltration less frequently, possibly because when the lesion reached the intima it spread horizontally along it. Such changes make it easy to understand why secondary abscesses in the brain are so common in cases of bronchiectasis and abscess of the lung.

In no case in the present series were the large pulmonary vessels invaded from without, but Boswell³⁹ described a case in which infection spread to the main right pulmonary artery from an inflamed mediastinal lymph gland with which it was in contact. Death was due to occlusion of the affected portion of the artery by a thrombus.

III. *Invasion Through the Vasa Vasorum.*—This is rare but probably occurs occasionally in cases of pyemia in which the infection has gained access to the systemic circulation. Mehlin²⁰¹ described a case in which there was an abscess in the media of the stem of the pulmonary artery with much less polymorphonuclear infiltration of the intima and adventitia. A somewhat similar case (that of a man who died of pyemia after prostatectomy) occurred in the present series. There were many septic emboli in the pulmonary arteries, but several arteries containing no such emboli showed extensive polymorphonuclear infiltration of the media which destroyed the muscle and separated the elastic laminae but produced only minor changes in the intima and adventitia. In these cases though spread through the vasa vasorum was a possibility, it is much more probable that the infection reached the arteries from infected emboli in the lumen and for some reason spread more widely in the media than elsewhere.

IV. *Infection Reaching Pulmonary Vessels from Their Lumens.*—
A. *Spread from an Infected Embolus:* This is common, and 3 cases were noted in the present series. In 2 cases only large vessels were involved. The lumens contained clots infiltrated with polymorphonuclears. There was polymorphonuclear infiltration of the underlying intima and often more intense and widespread infiltration of the media with separation but not destruction of the elastic laminae. There was usually also some polymorphonuclear infiltration of the adventitia. In the third case (that of a man who died of sepsis after prostatectomy) many small muscular arteries contained thrombi in various stages of organization, in which were many polymorphonuclears and large mononuclears. There were many polymorphonuclears in the underlying thickened intima but none in the media. In a fourth case (that of a woman who died of pulmonary embolism after removal of the ovaries and tubes)

syphilitic aortitis was observed at autopsy. Many large pulmonary arteries were blocked by laminated, nonadherent, apparently uninfected thrombi. The right main pulmonary artery showed great thickening of the adventitia, which contained many fibroblasts, large mononuclears and capillaries with a swollen endothelium. Many of the thrombosed arteries and some without thrombi showed a similar subacute adventitial lesion, and others showed a more acute lesion, with an exudation of fibrin, red blood cells and some leukocytes and with collections of large mononuclears in the surrounding connective tissue. The lesion in the adventitia usually appeared older than the thrombi in the lumen, which were unorganized and not septic. The possibility that there may be a primary adventitial lesion (perhaps syphilitic) with secondary thrombosis must be considered. But organization of thrombi in large arteries may be long delayed, and perhaps the presence of thrombi in the lumen excites a reactive inflammatory lesion in the adventitia.

B. Direct Implantation of Infection in the Intima Without Preceding Embolism: Most of the cases that have been reported in the literature were of this type, but no such case occurred in the present series. The cases may be subdivided according to the presence or absence of special strain on the pulmonary arteries which predisposes them to infection. In the following cases there was no special strain on the pulmonary arteries, but infection usually occurred in the course of an acute specific fever.

(a) In cases of influenza Obendorfer²²⁰ and Corten⁶¹ said that the primary lesion is necrosis of the small pulmonary vessels with thrombosis followed by suppurative arteritis and hemorrhages into the surrounding lung tissue. The hemorrhages then become secondarily infected, and sepsis dominates the clinical and pathologic picture. Others³⁷ have expressed the belief that suppurative pneumonia is primary and that the vascular lesions are secondary.

(b) A case of gonorrhea was described by Fürth¹¹⁰ in which septicaemia and multiple pulmonary embolisms followed gonorrhea, and the patient died of congestive heart failure. At autopsy no evidences of infective endocarditis were found. There was a partly organized, infected thrombus in the stem of the pulmonary artery. Fürth said that he thought that the primary lesion was gonococcic endarteritis with secondary thrombosis, but the evidence for this diagnosis seems insufficient.

(c) Mehlin,²⁰¹ in a boy who died of typhoid, observed extensive acute suppuration in the intima of the stem of the pulmonary artery and a less extensive and a more chronic type of lesion in the media and adventitia.

In most of the cases reported due to direct implantation there was strain on the pulmonary arteries predisposing to infection. The strain may be due to a congenital or an acquired lesion.

The commonest congenital lesion is patent ductus arteriosus.^c Abbott¹ said that 21 of 92 patients with a patent ductus arteriosus died of infective endarteritis. The signs of infective endocarditis, with special incidence of emboli in the lungs, became superimposed on those of the original congenital defect. The pulmonary artery, its main branches and the patent ductus were filled with a grayish friable clot. There was often secondary infective endocarditis of the pulmonary and tricuspid valves and sometimes a fusiform aneurysm of the pulmonary artery. The clot and the underlying wall of the artery were densely infiltrated with leukocytes. Mehlin²⁰¹ described a similar case in which there was an accessory cusp to the pulmonary valve but not a patent ductus. No doubt in these cases the infective endarteritis was primary and the thrombosis secondary.

With regard to acquired lesions, French authors have described acute pulmonary arteritis in cases of mitral stenosis.^d After an infection, prolonged pyrexia, anemia, cyanosis, dyspnea and repeated hemoptyses occurred and the patient dies in a few weeks of marasmus and asphyxia. In cases in which heart failure is already present when infection occurs, the signs of infection are not clinically obvious, but death soon occurs from rapidly progressive heart failure. At autopsy widespread thrombosis of the pulmonary arteries is often observed. In places not covered by thrombus there are so-called fibrinoleukocytic vegetations on the ulcerated surface of atheromatous patches. These showed beginning organization and contained gram-positive cocci. Such cases have been described only in the French literature. Probably the presence of the cocci is due to agonal invasion of the blood stream and the lesions are really rheumatic.

Comment.—Thus, pulmonary arteritis occurs as a serious complication in a large proportion of cases of patent ductus arteriosus. Its occurrence in cases of acquired cardiac disease is not established, and its importance there is certainly not great. It occurs in every case of pyemia with septic pulmonary emboli but is only an incident in the condition and probably is of little direct importance, though possibly occasionally the affected artery may rupture, causing fatal hemorrhage. Pulmonary arteritis also occurs in all cases of suppurative pulmonary disease, and in these cases involvement of the pulmonary veins may be the cause of metastatic abscesses in the brain and elsewhere.

(c) 35, 118, 259, 269.

(d) 59, 160, 165, 183.

PERIARTERITIS NODOSA

Periarteritis nodosa is rare in the pulmonary vessels. Sternberg²⁸⁷ described 1 case and said that only 2 others have been reported. Her patient had been pyrexial for one week, and there were signs of consolidation at the base of the left lung. She died following profuse hemoptysis. At autopsy the lower lobe of the left lung and the left pleura were full of blood. The walls of the small and large pulmonary arteries were necrotic, and they and the surrounding lung tissue were infiltrated with leukocytes. The diagnosis of periarteritis nodosa does not seem to be fully established in this case.

PRIMARY NEOPLASMS

The occurrence of a primary neoplasm of the pulmonary vessels is rare, records of only 2 cases having been found in the literature.^e Both patients died of congestive heart failure. In the first case, that of a man of 68, the stem of the pulmonary artery was filled by an adherent, dense yellowish mass which spread into the main branches. Microscopically it was a malignant leiomyoma. In the second case, that of a child of 3½ years, there was a simple leiomyoma growing from the left pulmonary vein.

SECONDARY NEOPLASM

Secondary neoplasm of the pulmonary vessels occurs much more frequently and there were 8 examples in the present series. The tumor may reach the pulmonary vessels either by embolism or by invasion from without.

TUMOR EMBOLISM

Tumor embolism is rare. Reports of 3 cases have been found in the literature, and there was 1 case in the present series. In 2 of the cases reported^f a patient with carcinoma of the stomach died of congestive heart failure for no apparent reason. At autopsy the only change observed in the heart was slight hypertrophy of the right ventricle. Microscopically many of the small pulmonary arteries were thrombosed. In some arteries the thrombus was completely organized and showed no less degenerate carcinoma cells, and in still others well preserved tumor cells lay free in the lumen. The presence of tumor cells in the lumen causes thrombosis, and ultimately the obstruction to the pulmonary arteries in these cases was attributed to the tumor that was present in this way. In 1 case²⁷¹ the only tumor that was present in the lungs was within the vessels. In the other cases there was also a

(e) 99, 140.

(f) 151, 271.

great deal of tumor in the peribronchial and perivascular lymphatic vessels. In the third case ³²⁷ the patient died of carcinoma of the pancreas. At autopsy masses of carcinoma cells embedded in thrombus were present in the endocardium of the tricuspid valve and the right ventricle and in some of the small pulmonary arteries. As the thrombus organized, the tumor cells died.

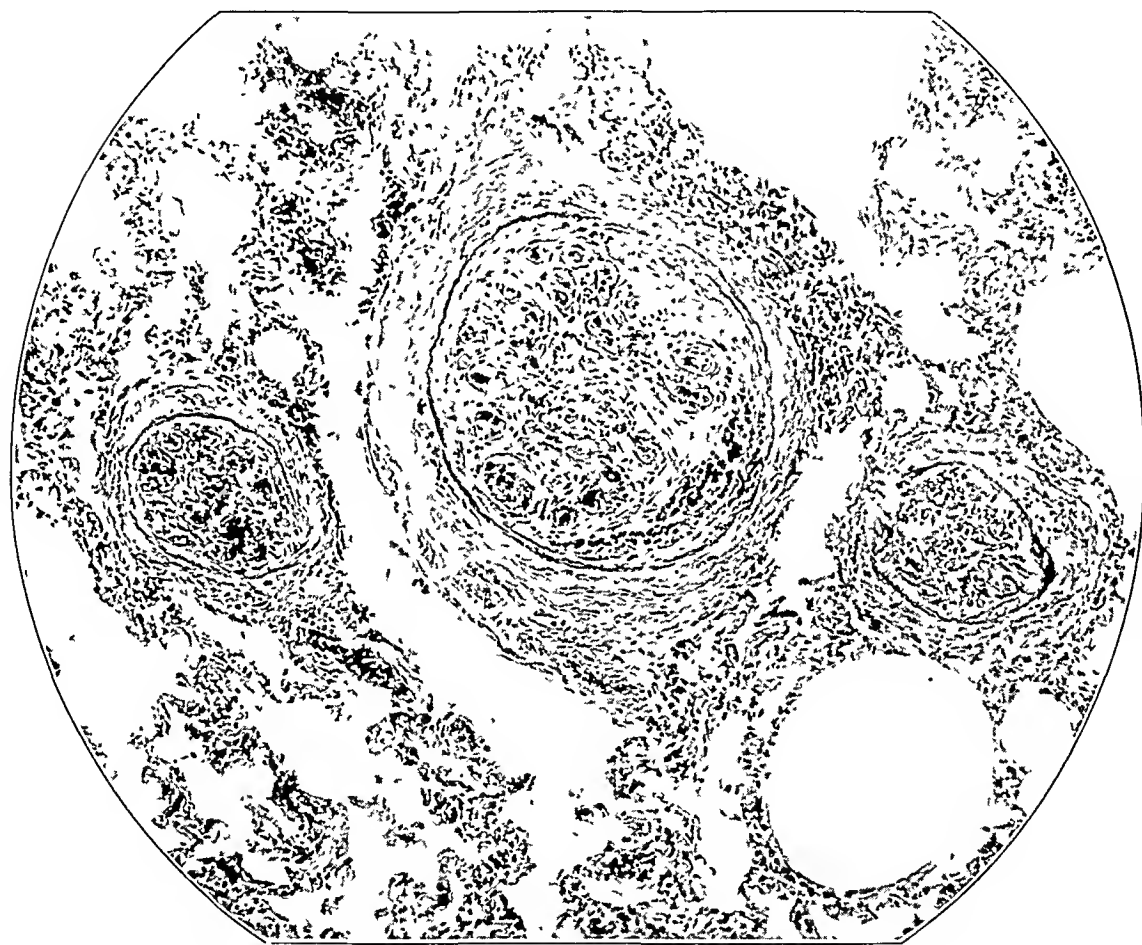


Fig. 33.—Photomicrograph of a section of a tumor embolism of the pulmonary arteries ($\times 115$; stained with methylene blue and eosin). Three small pulmonary arteries filled with organized recanalized thrombus and containing clumps of carcinoma cells are shown.

The patient in the present series was a man of 64 with extensive abdominal carcinomatosis. The primary growth was not found. At autopsy no secondary deposits were seen in the lungs. The heart was slightly enlarged as a result of hypertrophy of the left but not of the right ventricle. Coronary arteriosclerosis was observed.

Microscopically (fig. 33) several small pulmonary arteries in both lungs showed tumor emboli. The growth was confined to the lumen of these vessels. There was none in the pulmonary parenchyma. In some vessels the carcinoma cells lay

loose in the lumen, but even in these the intima showed marked thickening by lamellar connective tissue. In most cases the lumen was blocked by an organized and canalized thrombus containing clumps of more or less degenerate tumor cells. In a few cases the organization was of longer standing, the connective tissue being dense and hyaline, and no tumor cells were visible. In one artery there was an outer layer of the intima consisting of dense hyaline connective tissue without tumor cells and a thicker, more cellular, inner layer of organized thrombus containing degenerate tumor cells. In this artery there was thus evidence of three superimposed tumor embolisms of different ages. Some of the arterioles near the affected arteries, obviously branches of them, showed similar changes.

It is probable that tumor embolism of the pulmonary vessels is commoner than is usually supposed but is missed in the absence of thorough microscopic examination, as there are no gross changes. The tumor cells may enter the veins of the primary growth directly or they may travel along lymphatic vessels to enter the veins through the thoracic duct and so be carried to the lungs. Probably usually, as in the cases here reported, the involvement of the pulmonary vessels is of no great consequence, but occasionally it may be so extensive as to embarrass the heart and even cause death from heart failure.

INVASION FROM WITHOUT

Invasion from without is much commoner and occurred in 7 cases in the present series. The commonest site was the perivascular lymphatic vessels, which sometimes were widely involved and thus much more conspicuous than in health. In 2 cases the deposits were confined to this site, but in 5 cases the other coats of some vessels were involved.

Large Arteries.—Apart from deposits in the perivascular lymphatic vessels, the large arteries were involved in only 1 case, that of a man of 25 with multiple myelomas and a large mediastinal mass invading the lungs. In that case an artery 8.4 mm. in diameter showed extensive infiltration of all the coats by tumor, which separated and in places destroyed the elastic laminae of the media and formed large masses in the intima. In many other arteries the perivascular lymphatic vessels were full of tumor growth.

Small Arteries.—These were involved in the foregoing case and in a case of sarcoma of the leg with secondary mediastinal deposits invading the lung. In both cases many small arteries showed deposits in the adventitia. Many showed endarteritis, the intima being greatly thickened by loose connective tissue containing many lymphocytes and large mononuclears and a few polymorphonuclears. A few capillary lumens also were present. Most of these vessels showed many tumor cells among the round cells. These usually seemed to penetrate to the intima through the media, which was also infiltrated, but sometimes the tumor grew

along the intima for long distances, forming a column of growth hollowed out for the passage of blood. Such an artery, if cut transversely, sometimes showed growth in the intima and little or none in the media and adventitia, though almost certainly the growth originally grew into the intima through the media.

Arterioles and Venules.—These were affected in the case of multiple myeloma. In many instances the walls were greatly thickened and consisted of delicate fibrillar connective tissue infiltrated with growth. The lumen was often greatly narrowed.

Capillaries.—These were also involved in this case. The tumor invaded the alveolar walls, and many alveolar capillaries were blocked by the growth.

Small Veins.—These were involved in 4 cases: the cases of multiple myeloma and secondary sarcoma just mentioned, a case of carcinoma of the stomach in a man of 50 and a case of Hodgkin's disease in a man of 72. Tumor was commonly present in the adventitia, and the walls were infiltrated from without, often with an accompanying endophlebitis similar to the inflammatory reaction in the small arteries. The greatly thickened wall of the vein consisted of delicate fibrillar connective tissue with many lymphocytes, large mononuclears and capillary lumens as well as tumor cells. The lumen was often considerably narrowed and in the case of sarcoma was often completely obliterated by necrotic tumor tissue. In some cases the necrotic tumor showed beginning organization with the ingrowth of new capillaries and fibroblasts. In the case of myeloma the tumor often grew for long distances along the intima, and there was great narrowing of the lumen, while little or no tumor was present in the media or adventitia. Possibly there the tumor had reached the veins by extension from the blocked capillaries in the alveolar walls. Fried¹⁰⁷ also mentioned the tendency for a tumor to grow along the veins. Perhaps the common involvement of the veins accounts for the frequency of cerebral metastases in cases of intrathoracic neoplasm.

Large Veins.—These were involved in only 1 case. There were metastases from a carcinoma of the pancreas in the perivascular lymphatic vessels, and they had just begun to invade the media.

COMMENT

With regard to the influence of neoplasm on the occurrence of pulmonary arteriosclerosis, Jores¹³⁸ said that in patients with carcinomatous deposits in the perivascular lymphatic vessels thrombosis of the small pulmonary vessels may occur. This opinion was based chiefly on a case described by Rössle.²⁵² In the present series 2 patients with

perivascular deposits showed marked sclerosis of the affected vessels, and in 2 others organized thrombi were present. But these changes were so common in the absence of tumor that no conclusions can be drawn. There is no doubt, however, as to the association with endarteritis and endophlebitis in the cases of myeloma and sarcoma, in which the intima of the small arteries and veins that were invaded by growth showed great thickening, with the presence of new capillaries, lymphocytes and large mononuclears and sometimes polymorphonuclears.

Thus, on the whole, invasion of the pulmonary vessels by tumor is usually of no clinical importance, though invasion of the veins may be associated with the development of cerebral metastases. Occasionally extensive tumor embolism of small arteries or large primary myomas of the walls of the large vessels may obstruct the circulation. The pressure of mediastinal tumors on the pulmonary vessels has also been described as an occasional cause of failure of the right side of the heart.⁸

THROMBOSIS OF THE PULMONARY VESSELS INCIDENCE

Many individual cases have been described, but there have been few systematic studies of thrombosis of the pulmonary vessels. The most important paper was Møller's.²⁰⁷ He said that Lubarsch in 1,932 autopsies noted 347 cases of pulmonary embolism (18 per cent) and 16 of pulmonary thrombosis (0.9 per cent). On careful examination of the lungs in 176 autopsies Møller noted thrombi in 51 cases (29 per cent), and in these 51 cases 84 thrombi were present. Billings³² observed 11 thrombi in 1,700 autopsies (0.7 per cent). In the cases described in the literature the large intrapulmonary arteries were chiefly involved. In the present series of 100 consecutive unselected autopsies in which the pulmonary vessels were thoroughly investigated, thrombi were observed in 28 cases, which compares well with the 29 per cent reported by Møller. It is clear that thrombi are commonly present at autopsy but that only careful search will reveal them in many cases. This accounts for the widely different estimates of their frequency given by various authors.

THROMBI IN THE STEM OF THE PULMONARY ARTERY

The only case of thrombus in the stem of the pulmonary artery in the present series was that of a man of 72 who died of pulmonary embolism. A recent nonadherent thrombus spread back from the embolus to the stem of the pulmonary artery, but this was obviously agonal.

(g) 163, 164, 182.

Records of 26 cases have been found in the literature.^h In 6 of theseⁱ the stem of the pulmonary artery was said to be completely blocked by an old partly organized thrombus. Hart¹³⁰ and others suggested that when the stem of the pulmonary artery is gradually blocked by a slowly forming thrombus the circulation through the lungs may be maintained by the widening of the collateral anastomotic channels between the pulmonary and the bronchial vessels. But it is clear that normally complete blockage of the stem of the pulmonary artery must bring the circulation to an end, no matter how slowly the thrombosis develops or how extensive the collateral circulation through the bronchial vessels may be, since the blood which enters the right heart through the systemic veins will be unable to leave it. The only circumstance in which this need not occur is when there is a patent interauricular or interventricular septum. The blood which enters the right side of the heart may then pass directly to the left side and be carried to the lungs through the dilated bronchial arteries and their anastomoses with the pulmonary capillaries. The patient may be able to live, but he will be profoundly cyanosed, owing to the admixture of venous with arterial blood. But abnormal communications between the two sides of the heart were mentioned in only 2 cases,^j in both of which a widely patent foramen ovale was present. In 1 case¹⁷⁹ the foramen ovale was found at autopsy to be occluded by a thrombus of recent development, and the patient's sudden death was attributed to this. In the cases in which no abnormal communication was present either the complete occlusion of the artery was due to sudden thrombosis immediately before death in addition to an old parietal thrombus, or during life the thrombus actually did not completely occlude the pulmonary artery, but after death the wall of the artery contracted down so as to come in contact with it. A small lumen is all that is necessary to maintain life. In acute experiments on dogs it has been noted that the systemic blood pressure is not reduced until the cross-sectional area of the stem of the pulmonary artery has been reduced by from 61 to 86 per cent, and death does not occur until the area has been reduced by from 84 to 96 per cent.¹¹² Probably in cases of gradually developing thrombosis the cross-sectional area of the lumen may be reduced even more without causing death, so that a scarcely perceptible chink may suffice to maintain life. Even in the cases in which the foramen ovale was patent it is doubtful if the occlusion of the pulmonary artery was complete, since cyanosis was only slight.

(h) 33, 35, 75, 110, 117, 118, 130, 139, 175, 179, 186, 201, 208, 238, 259, 269, 273, 285, 292, 309.

(i) 35, 75 (case 2), 130 (2 cases), 269, 309.

(j) 179, 309.

In all cases the thrombus was old, adherent and often laminated and partly organized. The heart at autopsy sometimes showed various acquired or congenital lesions, such as mitral stenosis and patent ductus arteriosus, with the changes in the size of the cavities usually associated with these lesions. In most but not all of the patients with no such lesions there was some cardiac enlargement, often especially of the right side. The lungs usually showed merely congestion and edema, though sometimes one or more infarcts were present.

Symptoms.—Symptoms had been present for from one month to several years, but it was difficult to distinguish the symptoms due to the pulmonary thrombus from those of the underlying disease of the heart (which was usually present) and other conditions. In cases of embolism of large pulmonary arteries the heart was usually found to be laboring with a rapid regular rate and accentuation of the pulmonary second sound.³²³ In some cases there were to-and-fro murmurs over the pulmonary artery, perhaps due to dilatation of the fibrous ring about the pulmonary valve or to close approximation of the engorged vessel to the wall of the chest. Signs of failure of the right side of the heart were sometimes present. The electrocardiogram in some cases showed a prominent Q and an inverted T wave with a somewhat high origin in lead III, suggesting occlusion of the coronary artery. The clinical features sometimes also closely resembled those of occlusion of the stem of the pulmonary artery, however, there was no sudden onset of symptoms to suggest embolism. Dyspnea on exertion was always present but was sometimes slight. Cyanosis was usually present but sometimes was absent.^k The heart was usually enlarged even in the absence of independent cardiac disease, but sometimes there was no clinical enlargement.¹ Occasionally the thrombosed pulmonary artery threw a particularly dense shadow on the roentgenogram.³⁰⁹

Most patients died of gradually progressive heart failure. In 2 cases death was sudden: in 1 case^{231f} there was hemoptysis, attributed to the closure of the patent foramen ovale by a thrombus; in the other²⁸⁵ there was an attack of cardiac pain. In 2 cases death was due to intercurrent disease (pneumococcic meningitis³³ and pyelonephritis secondary to tabes dorsalis¹³⁰).

It is thus clear that the condition can rarely be diagnosed during life. The onset is gradual, and the symptoms are those of ordinary congestive heart failure, which might well be due to the underlying cardiac disease, which is usually present. Sometimes the symptoms are so slight that the patient dies of intercurrent disease and there is little to draw attention to the cardiovascular system.

(k) 35, 118, 130.

(l) 139, 238.

THROMBOSIS OF THE MAIN RIGHT AND LEFT
PULMONARY ARTERIES

In 3 cases in the present series thrombosis was present in the main right and left pulmonary arteries. In all the cases the thrombi were recent and unorganized.

The first patient, a man of 51, died in ten minutes of pulmonary embolism seventeen days after cholecystectomy. The right and left pulmonary arteries and the artery to the lower lobe of the right lung contained slightly adherent unorganized thrombi, undoubtedly embolic.

The second patient was a woman of 52 with a blood pressure of 176 systolic and 90 diastolic, syphilitic aortitis and a slightly enlarged heart. She died in a few hours with pain in the right side of the chest, tachycardia and râles at the base of the right lung sixteen days after an operation for mastitis. The right pulmonary artery was occluded by a thrombus which was slightly adherent to the posterior wall. This extended, gradually tapering, for about 6 cm. into the branch to the lower lobe of the right lung. There was a separate and apparently older thrombus in the branch to the upper lobe. Several small thrombi in smaller branches were present in the upper lobe of each lung. All were unorganized, but there was chronic or subacute periarteritis, older than that in the thrombi, in many of the thrombosed vessels. The thrombi were probably embolic but possibly may have been secondary to the periarteritis and were formed in situ.

The third patient, a man of 72, sixteen days after amputation of the left leg for gangrene, suddenly became cyanosed from the level of the nipples upward. Respiration was slow and labored, and there was marked bulging of the veins of the neck and face. He died in a few minutes. There was a large thrombus in the left iliac vein and a large unorganized clot extended from the right ventricle to the stem of the pulmonary artery and its right and left branches. This was undoubtedly an embolus with superimposed thrombosis.

Many cases of thrombosis of the main artery to one or both lungs have been reported.^m The main artery to one or the other lung was thrombosed in 11 (6 per cent) of Møller's 176 consecutive cases at autopsy. Often one artery was completely blocked.ⁿ In a few cases both pulmonary arteries were completely occluded.^o This is no more compatible with the continuance of the circulation than is occlusion of the stem of the pulmonary artery unless there is an abnormal communication between the two sides of the heart or a patent ductus arteriosus. Here, too, it is probable that the occlusion was completed by a terminal acute thrombosis superimposed on a chronic thrombosis immediately before death or that a small lumen, which escaped detection, actually was present. In many cases the thrombus in one or both arteries was parietal, allowing an appreciably free lumen. In most cases the thrombi were old, laminated and partly organized. In 1 case¹⁴¹ the

(m) 24, 32, 33, 39, 75, 76, 98, 117, 118, 130, 131, 139, 141, 170, 175, 177, 179, 183, 186, 200, 201, 207, 208, 231, 235, 238, 260, 262, 263, 269, 282, 285, 292, 309, 311,

(n) 39, 75, 130, 141, 199, 231, 235, 292.

(o) 75, 179, 309.

organization was complete, and the left pulmonary artery from its origin to the hilus of the lung consisted of a cord of dense fibrous tissue containing many capillary lumens.

Symptoms.—In most cases there were no symptoms pointing to the sudden occlusion of a large pulmonary artery, though in some cases ^p the patient, who had been ill for weeks previously, died suddenly or within a few hours, with pain in the chest, dyspnea and cyanosis. In those cases the thrombus was old and partly organized. Probably, therefore, the terminal symptoms were due to sudden thrombosis superimposed on an old thrombus with sudden completion of the occlusion of the lumen. In a few cases, in patients previously well or suffering from diseases not connected with the cardiovascular system progressive and ultimately fatal heart failure was initiated by the sudden onset of symptoms, such as dyspnea, cyanosis, hemoptysis and pain in the chest, and in some of those the patient also died suddenly. In those cases no doubt the onset of symptoms was due to the completion of the occlusion of the pulmonary artery, and the sudden death was due to pulmonary artery, and the sudden death was due to the completion of the failure had previously been present but suddenly became worse. It is difficult to say whether or not the initial heart failure was due to pulmonary thrombosis, but no doubt the thrombosis caused the final accentuation of the symptoms.

In all the other cases there were no symptoms pointing to pulmonary thrombosis, and occasionally ^r there were no circulatory symptoms at all, the patients dying of intercurrent disease. In most cases the first symptoms were those of gradually increasing heart failure, though occasionally repeated hemoptysis ^s or pyrexia was the first symptom. Dyspnea was nearly always, and cyanosis usually, present at some stage. The lungs usually showed only the physical signs of passive congestion or of independent pulmonary disease, but occasionally there were areas of feeble breath sounds, an impaired percussion note and pleural friction over areas where infarcts were later found. The heart was usually a little enlarged and sometimes showed the signs of independent cardiac disease. Occasionally the pulmonary second sound was accentuated or even followed by the diastolic murmur of pulmonary incompetence, ¹⁸³ but usually the pulmonary second sound was not remarkable or was even weaker than usual. ²⁰⁰ Occasionally there was a loud systolic murmur transmitted to the lung supplied by the thrombosed artery. ¹⁴¹ Roentgenograms often showed special prominence of the

(p) 39, 235, 260.

(q) 32, 75, 183, 262.

(r) 33, 131.

(s) 98, 311.

pulmonary artery and sometimes dense shadows corresponding to the thrombosed vessel.^t The electrocardiogram usually showed no abnormality or else changes associated with independent cardiac disease, but occasionally there was right axis deviation.ⁿ Death was almost always due to gradually progressive congestive heart failure, though occasionally it was sudden.

Postmortem Observations.—At autopsy the heart occasionally appeared normal.^v Often there was independent rheumatic, syphilitic or congenital cardiac disease. Occasionally there was marked hypertrophy of the right ventricle for which no cause other than the thrombosis could be found.^w In other cases the right ventricle was of normal thickness. This was especially noteworthy in Karsner's case of complete obliteration of the left pulmonary artery by an organized thrombus,¹⁴¹ in which the absence of hypertrophy of the right ventricle, in spite of complete occlusion of the left pulmonary artery of long standing, was striking. In spite of the occlusion of the artery the lungs always showed congestion and rarely infarction.

Thus, in cases of thrombosis or chronic embolism of the main artery to one lung distinctive symptoms were unusual. In most instances the patient showed gradually progressive heart failure without a sudden onset, and the symptoms usually appeared either in the course of pre-existing heart failure or in patients in whom independent cardiac disease in itself made them liable to heart failure. Therefore, thrombosis can rarely be diagnosed.

THROMBOSIS OF THE LARGE INTRAPULMONARY BRANCHES

Thrombosis of the large intrapulmonary branches of the pulmonary artery occurred in 13 cases in the present series. In 10 the thrombi were seen macroscopically, and in 3 they were discovered microscopically. The cases were as follows:

CASE 1.—A woman of 78, who had had both feet amputated because of gangrene seven years before, was cyanosed and dyspneic. There was edema of the legs and ascites. The blood pressure was 180 systolic and 100 diastolic. The heart was enlarged. At autopsy the portal vein was thrombosed. There was hypertrophy of the left but not of the right ventricle. The lungs were congested and edematous without infarcts. No thrombosed arteries were seen grossly, but microscopically an artery 2.5 mm. in diameter in the right lung was observed to be blocked by a thrombus composed of fused platelets, red cells, white cells and fibrin and to show many areas of early organization, as indicated by the ingrowth of new capillaries and fibroblasts. It is doubtful whether the thrombus was embolic or had formed in situ.

(t) 39, 309.

(n) 24, 139.

(v) 75, 263.

(w) 24, 139, 292.

CASE 2.—A child aged 13 months died of generalized tuberculosis. There was a large cavity in the upper lobe of the right lung. An artery near this was converted into a fibrous cord. Microscopically a completely organized thrombus was seen. In this case the thrombus was no doubt the result of the presence of a cavity in the immediate neighborhood.

CASE 3.—A man of 73 had emphysema. After removal of a vesical tumor bronchopneumonia developed and he died. The heart weighed 450 Gm. and the right ventricle was slightly thickened (5 mm.). There were thrombi in the perivesical veins. A firm, pale, adherent thrombus occluded the branch of the pulmonary artery to the lower lobe of the left lung for 2 cm. beyond its origin. Beyond that it was capped by a recent nonadherent clot. Old thrombi extended into some of the primary branches of the artery. Similar old thrombi were present in arteries about 5 mm. in diameter in the upper lobe of the left lung and the middle and lower lobes of the right lung. Microscopically the thrombi were seen to be organized at their base, with the ingrowth of new capillaries and fibroblasts. There were masses of large pigment-filled cells at the periphery. Evidently there had been an embolism from the pelvic veins with secondary superimposed thrombosis. Organization was well advanced, showing that the clots had been in situ for several days. Though the blood supply of the whole lower lobe was cut off, there were no symptoms of embolism and no infarcts.

CASE 4.—A woman of 87 with chronic fibroid pulmonary tuberculosis and emphysema had progressive dyspnea and edema for one and one-half years. The right ventricle was slightly thickened (5 mm.). There was a thrombus in the inferior vena cava. The artery to the lower lobe of the right lung was occluded for about 5 cm. by a firm, white, adherent thrombus, organized at its base and extending into the main branches. The lumen of an artery 5 mm. in diameter in the lower lobe was almost occluded by a thrombus of red blood cells and fibrin. The surface of the thrombus was covered by proliferated endothelium, and there was an early ingrowth of fibroblasts and new capillaries. Here, too, there was probably embolism with secondary thrombosis. There were no symptoms of embolism and no infarcts.

CASE 5.—A man of 51 suddenly became dyspneic and cyanosed and died in ten minutes sixteen days after cholecystectomy. Nonadherent clots were present in the right and left main pulmonary arteries, and a parietal thrombus, also unorganized, was present in the artery to the lower lobe of the right lung. The clots were undoubtedly embolic.

CASE 6.—A man of 50 died of carcinoma of the stomach with deposits in the lungs and bronchial glands. No obvious source of embolism was seen at autopsy. The heart was normal; the right ventricle was of normal thickness. Branches almost occluded by a firm, adherent thrombus, and a larger artery in the lower lobe of the right lung showed a parietal thrombus from 3 to 4 mm. thick. Microscopically the thrombi were laminated and showed early organization. There was ingrowth of connective tissue containing new capillaries, fibroblasts and pigment-containing mononuclears. Several arteries 3 or 4 mm. in diameter in the left lung were greatly narrowed by thrombi, some with early and some with advanced organization. Some of the thrombi that showed advanced organization were attached to the wall of the vessel by a stalk of dense fibrous tissue containing fine elastic fibers in its long axis. In this case the thrombi were perhaps formed in situ.

CASE 7.—A woman of 48 died of mediastinal abscess. A pulmonary artery 1.3 mm. in diameter showed extensive leukocytic infiltration of its walls, and its lumen was blocked by a septic embolus consisting of fibrin with many pus cells.

CASE 8.—A man of 43 died of syphilitic aortic incompetence and syphilis of the right pulmonary artery (previously described). The artery to the middle lobe of the right lung was blocked by an old adherent but unorganized thrombus. An artery 2.5 mm. in diameter showed at the origin of a large branch, which was almost occluded by an organized thrombus, a horn-shaped mass of fibrous tissue projecting for 1.4 mm. into the lumen. It had a core of dense pink-staining connective tissue and a superficial layer of less dense yellowish-staining connective tissue, with a sheaf of elastic fibers in the boundary zone. Both layers contained capillary lumens, many lymphocytes and large mononuclears and sheets of smooth muscle cells. This seemed to represent a completely organized thrombus projecting into the lumen from the mouth of a thrombosed branch. The presence of elastic tissue and smooth muscle was noteworthy. There was no obvious source of embolism, and the thrombi were perhaps formed in situ.

CASE 9.—A man of 69 had aortic stenosis and angina pectoris for eighteen years and congestive heart failure for three months. The heart weighed 700 Gm. The right ventricle was greatly thickened (12 mm.). A small, flat adherent thrombus was present in a large artery in the lower lobe of the left lung. The lumen of an artery 4.8 mm. in diameter was partly blocked by an organized thrombus (figs. 34 and 35). There were many recanalizing lumens, including five large ones (diameter, from 0.415 to 0.598 mm.). Each of these was surrounded by a thick elastic lamina inside which there was patchy intimal thickening up to a maximum of 0.18 mm. by loose connective tissue with many round, spindle and foam cells. There was thus atherosclerosis of the canalizing vessels. Between the lumens were broad sheets of smooth muscle, tending to surround them and form an irregular and incomplete media but also extending to other parts of the thrombus. Between the sheets of muscle cells there were loose fibrillar connective tissue and a little fine elastic tissue. The organized mass was papillary, and several papillae were cut so that they lay loose in the lumen. A part of the intima of the artery away from the thrombus was normal, but the rest was thickened and similar in structure to the organized thrombus. It probably represented an original parietal thrombus. In this case, too, the great development of elastic tissue and smooth muscle in the organized thrombus was noteworthy. There was no obvious source of embolism, but the normality of the intima away from the organized thrombus suggested that the thrombus may have been embolic in origin.

CASE 10.—A man of 56 died three weeks after suprapubic cystotomy. The lungs were emphysematous. The heart weighed 450 Gm., but the right ventricle was not thickened. There were recent nonadherent thrombi in vessels in both lungs. An artery 3.9 mm. in diameter contained a septic embolus, and its walls were invaded by leukocytes.

CASE 11.—A woman of 52 with a slightly enlarged heart and a blood pressure of 176 systolic and 90 diastolic had pain in the chest, tachycardia and râles in the right side of the chest and died in a few hours after the onset of these symptoms, sixteen days after an operation for mastitis. The heart weighed 400 Gm., and the wall of the right ventricle was 5 mm. thick. The right main pulmonary artery was occluded by a recent thrombus, extending for about 6 cm. into the branch to the lower lobe of the right lung. Several branches in the upper lobe of the right lung and one in the upper lobe of the left lung also were blocked by an unorganized thrombus. Many of the thrombosed arteries showed a

subacute or chronic periarteritis, obviously older than the thrombi. The clots were probably embolic, originating in the operative site, but possibly they were secondary to the periarteritis and formed in situ.

CASE 12.—A man of 72, sixteen days after amputation of the left leg for gangrene, suddenly became cyanosed, with dyspnea and bulging of the veins of the neck, and died in a few minutes. There was marked emphysema. The heart weighed 350 Gm., but the right ventricle was not thickened. There was a thrombus in the left iliac vein, and another extending from the right ventricle to the stem of the pulmonary artery, its right and left branches and their primary branches.

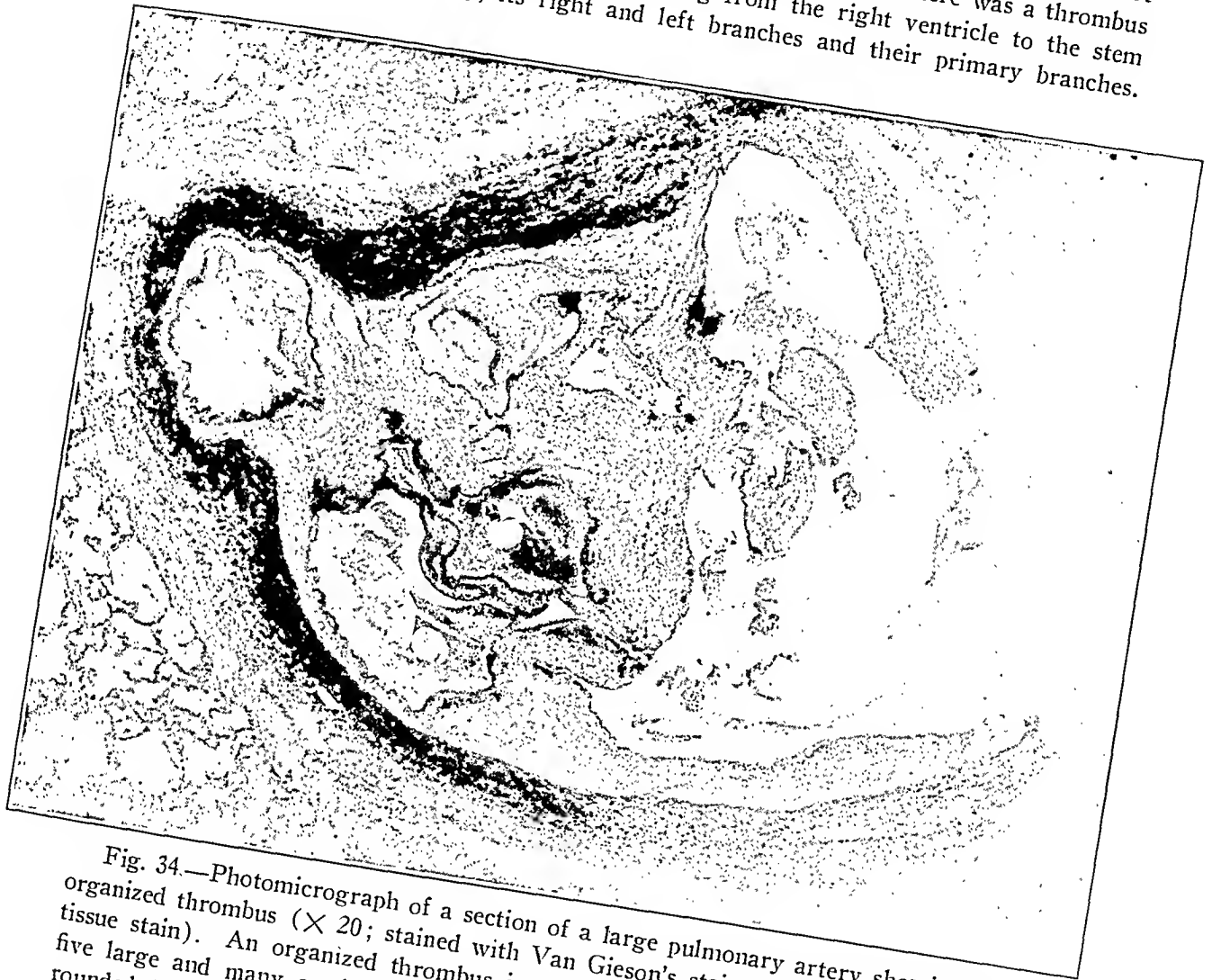


Fig. 34.—Photomicrograph of a section of a large pulmonary artery showing an organized thrombus ($\times 20$; stained with Van Gieson's stain and Verhoeff's elastic tissue stain). An organized thrombus is partly occluding the lumen. There are five large and many small recanalizing lumens. Each of the large ones is surrounded by an elastic lamina, inside which is an incomplete irregular layer of connective tissue. Between the lumens are sheets of smooth muscle set in loose connective tissue. The intima of the part of the artery not occupied by thrombus is normal above; below it is thickened by tissue similar in structure to that of the organized thrombus.

This was recent and unorganized. No doubt it represented an embolus with secondary thrombosis.

CASE 13.—A woman of 53 with ascites due to peritoneal metastases from an ovarian tumor died suddenly. There was no obvious source of embolism, though

an ovarian tumor had been removed twelve months previously, and embolism might have occurred after that. The heart was normal. An artery 3 mm. in diameter was almost occluded by a thrombus of platelets and fibrin, with an extensive ingrowth of capillaries and fibroblasts at its base and with its surface covered by proliferated intimal endothelium. The intima over about half the circumference was thickened by dense fibrous tissue containing a few capillary lumens, obviously representing an old organized parietal thrombus, perhaps due to embolism at the time of operation twelve months before. It may be that the recent thrombus was on the basis of the old lesion.



Fig 35—Enlargement of a portion of the artery shown in figure 34 ($\times 157$; same stain). In the upper left corner is a small part of the arterial media. The upper right portion of the figure shows a part of one of the canalizing lumens surrounded by an elastic lamina, inside of which there is slight, patchy thickening of the connective tissue. In the lower portion are irregular sheets of smooth muscle cells in the organized thrombus set in loose fibrillar connective tissue.

Summary.—Thus, thrombi were observed in the large intrapulmonary arteries in 13 of 100 consecutive autopsies. In 7 they were almost certainly embolic in origin, though often with superimposed secondary thrombosis. These were present either in patients dying of pyemia or in patients dying a few days after an operation. In 3 instances the patients died suddenly with symptoms of pulmonary embolism. In only 4 were there circulatory symptoms apart from those of pulmonary

embolism, and in each of these independent cardiac disease, capable in itself of causing the symptoms, was present. In 5 cases the thrombi were unorganized. The rest showed varying degrees of organization, with the presence of smooth muscle and elastic tissue in the most advanced cases.

Many cases of thrombosis of the large intrapulmonary arteries have been reported. Sometimes the thrombosis was widespread, involving all the arteries to one lobe^x or all the arteries of moderate size in both lungs.¹⁷⁷ The thrombi usually occluded the affected arteries, but sometimes they were parietal and they were then often situated on the spur at the bifurcation of an artery.²⁰⁷ Organization of parietal thrombi sometimes gave rise to bands stretching across the artery, attached to the vessel wall only by their ends or by one edge. Sometimes there were many such bands forming a network across the mouth of one or more branches.^y

Symptoms.—The symptoms in the cases reported were varied. Evidence of venous thrombosis was present in more than half the patients with large thrombi and in less than a third of those with small thrombi.²⁰⁷ Occasionally there was a sudden onset of symptoms, including dyspnea, cyanosis, hemoptysis or pain in the chest, followed by gradually progressive heart failure.^z But in most cases the symptoms were merely those of gradually increasing heart failure, which might well have been due to the underlying cardiac disease. Cyanosis was sometimes marked but was often slight or absent.^a Symptoms pointing to sudden occlusion of the pulmonary arteries were, as in the present series, more often absent than present. Möller²⁰⁷ said that symptoms such as sudden dyspnea, fainting, feeble pulse, pallor, pain in the chest and bloody expectoration were present in 22 of 23 patients with large thrombi which were directly fatal and in 21 of 42 patients with small thrombi not in themselves fatal. When there were small thrombi only one or two of these symptoms were present, and diagnosis was difficult. In 1 of Brenner's cases⁴² the patient, who had been slightly dyspneic for several months, suddenly became more dyspneic on the morning of his death. During the day he had four syncopal attacks accompanied with pallor and feeble pulse and died during the fourth attack. Four large arteries were occluded by thrombus, and no doubt each attack corresponded with the occlusion of one of these. In several other cases patients who had previously shown signs of heart failure died suddenly or rapidly with symptoms of heart failure.^b

(x) 186, 192.

(y) 207, 265.

(z) 32, 75, 98, 262.

(a) 32, 43, 192, 262.

(b) 32, 76, 183, 262.

Physical signs of independent pulmonary disease were commonly present. Occasionally there were signs due to infarcts (impaired percussion note, feeble bronchial breathing and pleural friction).^c Signs of independent cardiac disease were commonly present. In a few cases the heart was slightly enlarged. Occasionally there was marked accentuation of the pulmonary second sound,^d and in 1¹⁸³ there was a diastolic murmur of functional pulmonary incompetence. Occasionally the heart was apparently normal.^e Roentgenograms rarely helped in making a diagnosis, though occasionally a shadow representing a pulmonary infarct was present.^f The electrocardiograms never gave any help.

Course.—Death was almost always due to progressive heart failure. Occasionally it was sudden;^g occasionally it was due to intercurrent disease.^h The prominence of circulatory symptoms in the cases reported was no doubt due to the fact that in their absence the pulmonary arteries are rarely examined. In the present series in many cases there were no circulatory symptoms and the thrombi were discovered only on routine examination of the arteries. Probably the majority of thrombi in large intrapulmonary arteries cause no symptoms. At autopsy there was occasionally slight enlargement of the right side of the heart in the absence of independent cardiac disease. The lungs usually showed only congestion and edema, but sometimes there were infarcts.

THROMBOSIS OF THE SMALL MUSCULAR ARTERIES

Thrombosis of the small muscular arteries occurred in 19 cases in the present series. It is comparatively rarely mentioned in the literature, because it can be observed only with the microscope.

CASE 1.—A man of 68 had emphysema and a slightly enlarged heart. After suprapubic cystotomy pyrexia and auricular fibrillation developed, and he died in two weeks. At autopsy there was a suppurating periprostatis. There were septic infarcts in the lungs. The heart weighed 375 Gm., and the right ventricle was not thickened. Most of the small pulmonary arteries showed marked intimal thickening with narrowing of the lumen. Some were partly or completely blocked by thrombi in varying stages of organization, some consisting of red blood cells, leukocytes and fibrin, covered by proliferated endothelium and showing ingrowth of capillaries and fibroblasts at the base. In others the whole thrombus had been converted into a mass of connective tissue containing capillary lumens and many polymorphonuclears and large mononuclears, some full of blood pigment. Some of these, obviously representing organized parietal thrombi, projected into

(c) 32, 76, 139, 175, 192.

(d) 98, 183.

(e) 43, 139.

(f) 43, 139, 176.

(g) 43, 75, 179, 262, 285.

(h) 43, 74.

the lumen as horn-shaped masses of vascular cellular connective tissue. The recent thrombi were probably embolic, secondary to the periprostic suppuration. Possibly the older ones also were embolic, but they obviously dated from before the operation.

CASE 2.—A woman of 38 had pyemia after radium treatment for carcinoma of the uterus. There were an abscess of the broad ligament, thrombosis of the pelvic veins and septic pulmonary infarcts. Some of the small muscular arteries were blocked by recent emboli of fibrin and leukocytes.

CASE 3.—A woman of 68 died of pulmonary tuberculosis. The right ventricle was not thickened. In an artery 0.5 mm. in diameter a truncated cone of fibrous tissue, representing an organized parietal thrombus, projected for 0.16 mm. into the lumen over a base of 0.5 mm. Beneath it the elastica interna frayed out and disappeared, and the underlying media was replaced by dense connective tissue. There was no obvious source of embolism, and perhaps the thrombus was formed in situ.

CASE 4.—A woman, whose case was recorded previously as case 1 of thrombosis of the large elastic arteries, died at the age of 78. Many small arteries, from 0.16 to 0.75 mm. in diameter, were partly or completely blocked by dense connective tissue containing capillary lumens and sometimes showing a great deal of irregular elastic tissue. These represented old organized thrombi, possibly embolic in origin, which probably came from the gangrenous extremities seven years before.

CASE 5.—A woman of 67 died of cerebral thrombosis the day after one leg was amputated for gangrene. The lungs were emphysematous. The right ventricle was thickened (6 mm.). Two horn-shaped masses of dense connective tissue containing some longitudinal elastic fibrils projected into the lumen of an artery 0.42 mm. in diameter. These evidently were organized parietal thrombi, possibly arising as emboli from the gangrenous leg.

CASE 6.—A boy of 16 died of congestive heart failure. The heart weighed 500 Gm., and the right ventricle was thickened (6 mm.). There was no valvular lesion. There were two infarcts in the lower lobe of the right lung. A mass of dense connective tissue containing capillary lumens projected into and greatly narrowed the lumen of an artery 0.34 mm. in diameter. There was no obvious source of embolism.

CASE 7.—A man of 60, who had the right leg amputated for diabetic gangrene one year before, died of cerebral thrombosis two weeks after amputation of the left leg for gangrene. The right ventricle was normal. Two arteries 0.66 mm. in diameter were blocked by dense connective tissue containing capillary lumens. Evidently these were organized thrombi, possibly arising one year before as emboli from the gangrenous leg.

CASE 8.—A woman of 58 died of agranulocytosis. The heart weighed 500 Gm. The right ventricle was dilated. An artery 0.5 mm. in diameter was blocked by loose connective tissue containing two capillary lumens. Evidently this was an organized thrombus. There was no obvious source of embolism.

CASE 9.—A woman of 52 with a blood pressure of 170 systolic and 95 diastolic died of peritonitis. The heart weighed 425 Gm., and the right ventricle was 6 mm. thick. Two arteries, 0.30 and 0.42 mm. in diameter, were blocked by loose connective tissue containing fine elastic fibers, capillary lumens, red blood cells, lymphocytes, fibroblasts and pigment-containing large mononuclears. Another artery showed great uneven thickening of the intima of similar type, with extreme

narrowing of the lumen, probably due to an organized parietal thrombus. There was no obvious source of old emboli, and perhaps the thrombi were formed in situ.

CASE 10.—A man, whose case was recorded previously as case 6 of thrombosis of the large elastic arteries, died at the age of 50. Several arteries from 0.12 to 0.21 mm. in diameter were blocked by fibrous tissue containing from one to three capillary lumens. Several other arteries of the same size had their lumens almost exactly half occluded by a mass of dense connective tissue with a straight edge. In spite of the absence of capillary lumens, these were probably organized parietal thrombi. In several somewhat larger arteries (with a diameter of from 0.4 to 0.5 mm.) there were more recent thrombi of fibrin, platelets and leukocytes, with organization at the edges. In some of these the intima away from the thrombus was thickened and similar in structure to the organized part of the thrombus. Perhaps this represented organization of an older parietal thrombus.

CASE 11.—A man, whose case was recorded previously as case 8 of thrombosis of the large elastic arteries, died at the age of 43. The lumen of an artery 0.9 mm. in diameter was blocked by connective tissue with several capillary lumens, many round and spindle cells and strands of smooth muscle cells. The lumens of other vessels were blocked by loose cellular connective tissue with one or two capillary lumens. Others showed organized parietal thrombi of similar structure. Many of the thrombosed vessels showed portions of the media replaced by dense connective tissue, with round cells and new vessels. It is doubtful whether this was a syphilitic lesion (there was definite syphilis of the aorta and of a large pulmonary vessel) with superimposed thrombosis or whether it represented the ingrowth of vessels and connective tissue from the adventitia to the thrombus in the process of organization.

CASE 12.—A man with tumor emboli of some of the small pulmonary vessels, whose case was described under the heading tumor of the pulmonary arteries, died at the age of 53.

CASE 13.—A woman of 77 died of pulmonary and intestinal tuberculosis. The heart weighed 200 Gm., and the right ventricle was 2 mm. thick. In the dense apical tuberculous scars the intima of all the small arteries was greatly thickened by dense connective tissue, sometimes with complete obliteration of the lumen except for a few capillary lumens. In one artery a large part of the media was replaced by dense fibrous tissue. The thrombosis was probably a response to the surrounding tuberculous process.

CASE 14.—A man, whose case was recorded as case 9 of thrombosis of the large arteries, died at the age of 66. An artery 0.2 mm. in diameter and one of its branches as well as several surrounding arterioles were blocked by dense fibrous tissue, sometimes with a few capillary lumens. The thrombus appeared to have arisen in the parent artery and spread to the branches. There was no obvious source of embolism.

CASE 15.—A man, whose case was recorded previously as case 10 of thrombosis of the large arteries, died at the age of 56. An artery 0.55 mm. in diameter was almost obliterated by a mass of fibrous tissue with two capillary lumens. Another artery showed a horn-shaped mass of dense fibrous tissue projecting into the lumen. These probably represented organized parietal thrombi. They seemed to have been present for a longer time than the postoperative urinary infection.

CASE 16.—A man of 65 died of carcinoma of the pancreas with no circulatory symptoms. The heart was normal. A mass of dense fibrous tissue with a base

of 0.17 mm. projected for 0.14 mm. into the lumen of an artery 0.18 mm. in diameter. This probably was an organized parietal thrombus. There was no obvious source of embolism.

CASE 17.—A woman of 65 had carcinoma of the stomach and pulmonary tuberculosis but no circulatory symptoms. The heart was normal. A mass of dense fibrous tissue projected for 0.11 mm. on a base of 0.19 mm. into the lumen of an artery 0.25 mm. in diameter. This was probably an organized parietal thrombus. There was no obvious source of embolism.

CASE 18.—A man of 50 died of hematemesis. There were no circulatory symptoms. The heart was normal. A horn-shaped mass of fibrous tissue projected for 0.19 mm. on a base of 0.08 mm. into the lumen of an artery 0.76 mm. in diameter. Another similar mass in the same artery was cut transversely and seemed to lie loose in the lumen. The masses seemed to be organized parietal thrombi. There was no obvious source of embolism.

CASE 19.—A woman of 77 had auricular fibrillation and dyspnea for 5 months. The heart was normal, but syphilitic aortitis was present. An artery 0.27 mm. in diameter showed several masses of fibrous tissue, representing organized parietal thrombi, projecting into the lumen.

Thus, thrombosis of the small pulmonary arteries was commonly observed in the present series. It could be seen only on systematic microscopic examination of the lungs. Usually only a few arteries were involved, and probably if more blocks had been taken from each lung the condition would have appeared even commoner. In 5 cases the thrombi were almost certainly embolic. In the others there was no obvious source of embolism, and the possibility of their having been formed in situ must be considered. Circulatory symptoms were present in only 5 cases, and in all of these there was independent cardiovascular disease which amply accounted for them.

Thrombi in the small vessels were usually more completely organized than in the large vessels, perhaps because they were older. An alternative explanation is that the surface of the thrombus exposed to the ingrowth of new capillaries is relatively larger as compared with the volume of thrombus to be organized.

Thrombosis of the small pulmonary arteries has been reported relatively rarely, probably owing to the lack of systematic microscopic examination of the lungs, but a few isolated cases have been mentioned.¹ Occasionally the thrombosis was so extensive as to cause hypertrophy of the right ventricle and heart failure.

THROMBOSIS OF ARTERIOLES

Thrombosis of arterioles was found in only 3 cases in the present series, and in each case the thrombi seemed to spread from small

- (i) 20, 37, 61, 98, 107, 109, 117, 157, 179, 226, 300.
- (j) 117, 151, 271.

arteries of which the arterioles were branches. The cases are recorded as cases 4, 12 and 14 of thrombosis of small arteries. In each the thrombi were similar in structure to those in the parent vessels.

THROMBOSIS OF SMALL VEINS

Thrombosis of small veins occurred in 1 case in the present series.

The patient, a man of 56 with emphysema and acute superimposed on chronic rheumatic carditis, died of congestive heart failure. In one small vein the intima showed three sharply localized thickenings, the largest being 0.18 mm. long and 0.1 mm. thick. The thickenings consisted of loose connective tissue with many fibroblasts, large mononuclears and blood cells and a few elastic fibrils. The thrombosis could not have been embolic. Possibly stasis in the pulmonary veins, perhaps with a local rheumatic lesion of which no trace remained, determined the occurrence.

Thrombosis of pulmonary veins has rarely been reported. Isolated instances have been described in cases of pneumonia,^k pneumoconiosis²⁵⁶ and primary pulmonary venous sclerosis.⁹⁸ Some of the thrombi were organized and recanalized. Occasionally the mouths of the pulmonary veins were blocked by a thrombus in the left auricle in cases of mitral stenosis.¹ Apart from that, pulmonary venous thrombosis evidently plays only a small part in the pathologic conditions of the pulmonary circulation.

ETIOLOGY OF PULMONARY THROMBOSIS

In the present series there was an obvious source of embolism in 7 of the 13 cases of thrombosis of the large arteries and in 6 of the 19 cases of thrombosis of the small arteries. Probably the thrombi in these cases were embolic in origin, but that was absolutely certain only in the case of tumor embolism. In the cases in which there was no obvious source of embolism, emboli may have arisen from some unrecognized source, or the thrombi may have formed in situ. When embolism is the primary event, secondary thrombosis before and behind the embolus usually occurs, so that branching of the thrombus along the ramifications of the pulmonary artery does not disprove its embolic origin. Glynn¹¹⁶ expressed the belief that even thrombi that occur in septic conditions or after operations are really formed in situ. He described 8 such cases of what would ordinarily be called pulmonary embolism. All the patients died suddenly or rapidly. He adduced the following evidence in favor of the conclusion that the thrombi were formed in situ:

(k) 37, 248.

(l) 184, 273.

A. Macroscopic Appearances.—1. In all but 1 case the thrombus was laminated (but a laminated thrombus in a systemic vein may break off to form an embolus, though softer and more quickly formed coagulation thrombi are more likely to do so; ²⁴⁹ or a thrombus may gradually be deposited on a small pulmonary embolus).

2. In 5 cases there were thrombi in the small branches separate from those in the large (but this may have been due to multiple embolism or to stagnation in the small vessels distal to the obstructed large vessels).

3. It is impossible for laminated thrombi, which often extend into the terminal ramifications, to be deposited during the period of from five to thirty minutes between the onset of symptoms and death (but it is probable that no symptoms would arise from a moderate-sized embolus until enough secondary thrombosis had occurred to block a large part of the pulmonary arterial bed).

B. Microscopic Appearances.—1. In all the patients examined, hemosiderin had spread into the wall of the vessel, a change which requires days to develop. (This proves that the thrombi had been several days in situ, but it does not disprove that they had been carried there from a systemic vein.)

2. Three of the thrombi showed some organization (the same objection holds for this argument).

The opposite standpoint, that pulmonary thrombi are almost always embolic, was taken by Møller.²⁰⁷ In only 2 of his 51 patients, both with thrombo-arteritis secondary to local inflammation in the lung, were the thrombi undoubtedly formed in situ. Møller said that it is often possible to distinguish microscopically between autochthonous thrombi and old adherent emboli. The former are formed slowly; there are thick, closely set bands of platelets perpendicular to the wall of the vessel, and red blood cells are scanty. Emboli are usually formed by dislodged stagnation thrombi, which are rapidly formed and contain many red blood cells and no well formed bands of platelets. Dislodgment of agglutination thrombi, similar in structure to the autochthonous pulmonary thrombi, is rarer because they are more firmly adherent to the wall of the vein, and when it does occur, the bands of platelets are not perpendicular to the walls of the branch in which the embolus lodges. The presence of a great deal of iron in even a completely organized thrombus shows that it originally contained many red blood cells, so that it was of embolic origin. Using these criteria, he concluded that the great majority of the 84 thrombi in his 51 cases were embolic. Four were fresh stagnation thrombi. In 52 there was partial or complete organization, but there were remnants of fibrin and red blood cells and a great deal of iron pigment. Often iron pigment is observed in the wall of the vessel; so probably it is ultimately all removed. It is then impossible to decide

the origin of the thrombus or even to differentiate it from an arterio-sclerotic plaque. Often the amount of secondary thrombosis superimposed on the embolus is much greater than the original embolus; so it can be concluded with certainty that the clot was not embolic only if its whole extent is examined. In the case of 9 organized thrombi it was impossible to conclude whether the clots were embolic.

In the present series a much greater proportion of the clots were organized and contained little or no blood pigment. Moreover, it seems that Møller attached too much importance to the presence of old blood pigment. Some red blood cells are present in the most gradually formed clots, and even when the occlusion of the pulmonary artery is begun by an autochthonous agglutination thrombus, it commonly is completed, when the narrowing has progressed far enough, by a quickly formed stagnation thrombus containing many red blood cells, which when organized would contain a good deal of iron pigment. The frequency of nonoccluding parietal thrombi argues for formation in situ, since it might be expected that an embolus would travel until it reached an artery just small enough to be occluded. Møller, however, said that an embolus is often arrested by the spur at the bifurcation of an artery much larger than itself. He thus did not completely prove his point, though on the whole it is probable that most pulmonary thrombi are embolic. The lungs, as Aschoff pointed out, form a filter in the course of the circulation in which fragments of thrombus, growth, fat and other material ^m are arrested and prevented from entering the systemic arteries.

Nevertheless, many cases of undoubted autochthonous thrombosis have been described, under the following conditions:

1. In aneurysms of the pulmonary artery, congenital or syphilitic.ⁿ The thrombus is often laminated and partly or completely occludes the aneurysmal sac.

2. In acute pulmonary arteritis due to local disease of the surrounding lung ^o or complicating patency of the ductus arteriosus.^p

3. In syphilitic arteritis.^q Syphilitic aortitis, without aneurysm, is rarely associated with thrombosis, but the occurrence of syphilis and thrombosis at the same point in the pulmonary artery indicates that the thrombus is secondary to the arterial lesion.

Thrombosis has also been described in many cases of primary and secondary pulmonary vascular sclerosis. In the systemic circulation

(m) 190, 253.

(n) 32, 170, 175, 238, 292, 309, 311.

(o) 37, 39, 61, 220.

(p) 35, 110, 118, 259, 269.

(q) 57, 74, 141, 166, 192, 231.

thrombi often form over atheromatous ulcers, and there is no a priori reason why this should not be so in the pulmonary circulation. But atheromatous ulcers are rare in the pulmonary arteries and were not seen in the present series. In the absence of a broken endothelial surface or of sufficient narrowing of the lumen to cause stagnation, it is difficult to see why atheroma should cause thrombosis. Though in many cases no source of embolism was found, yet, since it is impossible to examine every systemic vein at autopsy, such sources may actually have been present. Therefore, while perhaps many of these cases are actually examples of autochthonous thrombosis, it is best to regard this diagnosis as nonproved.

Comment.—It is therefore probable that except in cases of pulmonary aneurysms, acute arteritis or syphilitic arteritis, in which autochthonous thrombosis may occur, most pulmonary thrombi are of embolic origin, though secondary thrombosis occurs before and behind the embolus. Except when a large embolism occurs in a septic condition with thrombophlebitis, or after an operation, and causes a large pulmonary infarct, the diagnosis is difficult, as the symptoms merge into those of congestive heart failure, which is often already present. Even large thrombi, if there is no independent cardiac disease, commonly do not cause any symptoms. If independent cardiac disease is present, it is possible that large thrombi may add somewhat to the load on the heart and so hasten the fatal issue. Small thrombi are common but probably of little importance.

ANEURYSMS OF THE PULMONARY ARTERY

Aneurysms of small pulmonary arteries in the walls of tuberculous cavities are common and are an important cause of copious hemoptysis. They will not be considered further here. Aneurysms of the stem and main branches of the pulmonary artery are rare, and Scott ²⁷⁸ said that only 90 cases have been reported since 1833. No cases were reported at autopsy at St. Bartholomew's Hospital between 1867 and 1912, though there were 350 cases of aneurysm in that period. Saccular aneurysms are exceedingly rare. Fusiform dilatation is commoner, but it is difficult to demarcate it from the simple dilatation so common in cases of pulmonary arteriosclerosis. In the present series there were several cases of marked dilatation of the stem and main branches, but none great enough to be called aneurysmal. In the case of syphilis of the pulmonary arteries, however, several of the smaller elastic and larger muscular arteries showed localized bulging of their walls where the media had been replaced by vascular fibrous tissue. There were no symptoms which could be referred to that. The cases reported in the literature may be classified as follows:

TYPES OF ANEURYSMS

1. *Traumatic*.—There was only 1 case in this group.¹⁹⁴ In that case there was a gunshot wound of the chest followed by pneumonia and later by repeated hemoptyses. There were dulness and bronchial breathing at the base of the right lung. There was a continuous murmur with systolic accentuation over the right lung. Roentgenograms showed a spherical mass at the root of the right lung. The patient died of hemoptysis. At autopsy an aneurysm the size of an orange was present on the right pulmonary artery about 4 cm. beyond the bifurcation.

2. *Mycotic*.—In several cases aneurysm was associated with infection of a congenital lesion (see the next paragraph). In addition, Salzer²⁶³ described the case of a woman of 60 who died of septicemia following pyelonephritis. The right pulmonary artery just before the hilus showed an aneurysm the size of a bean, filled with an adherent clot. The thrombus and the wall of the aneurysm showed a great deal of leukocytic infiltration. Evidently the aneurysm was due to the lodging of a septic embolus.

3. *Congenital*.—Ten cases have been collected from the recent literature. There were 5 cases in males and 5 in females, and the ages ranged from 4 to 49 years. In 4^r there was a patent ductus arteriosus; in 1 there was a widely patent foramen ovale,³⁰⁹ and in another,³³ stenosis of the infundibulum and a patent interventricular septum. In the others^s the congenital abnormality was thought to lie in the pulmonary artery itself. In no case was the diagnosis made during life. In 1¹⁰¹ there were no circulatory symptoms, and the patient died of tuberculosis. In 3^t there were only the signs of congenital cardiac disease complicated by infective endarteritis. In the others the signs of congestive heart failure were present, and in 3^u instances erroneous diagnoses of mitral stenosis and aortic incompetence were made. In only 1 were there signs of mediastinal pressure.³⁰⁹ In that case there were bulging of the manubrium sterni and paralysis of the left vocal cord, and the roentgenograms showed a rounded, nonpulsating mass in the region of the aortic arch. An erroneous diagnosis of mediastinal neoplasm was made. The patient (a girl of 19) was operated on, and the aneurysm was opened with immediately fatal results.

The cause of death in 1 case was pulmonary tuberculosis; in 1, rupture into the pericardium, and in 1, opening, at operation, of the aneurysm, which was mistaken for a neoplasm; in 3 cases, congestive heart failure, and in 3, superimposed infective endarteritis.

(r) 90, 101, 118, 269.

(s) 101, 175, 292.

(t) 33, 118, 269.

(u) 175 (2 cases), 309.

At autopsy the heart showed the congenital lesions previously mentioned. In the cases in which the only congenital lesion was in the pulmonary artery itself, the right ventricle was hypertrophied.

The aneurysm usually involved only the stem of the pulmonary artery. In Esser's case,¹⁰¹ that of a woman of 23, the stem of the pulmonary artery was as thin as paper and formed a thin-walled sac to within 1.5 cm. of the bifurcation, where it suddenly narrowed and became thicker. In Lissauer's¹⁷⁵ first case the pulmonary artery as far as the orifice of the patent ductus (which was also dilated) showed a bulge the size of an egg. Beyond the ductus the artery and both its main branches were greatly narrowed. In his second case the stem showed a bulge the size of a walnut to the left immediately above the cusps. The left pulmonary artery was obliterated, and the right was considerably narrowed. In the other cases reported there was merely fusiform dilatation of the stem of the pulmonary artery with or without dilatation of its main branches.

In cases of patent ductus arteriosus the pulmonary artery is always dilated, probably because of the increased pressure transmitted from the aorta. In 3 of the cases here reported there was infective endarteritis, which perhaps weakened the walls enough to allow further bulging. Lissauer attributed the aneurysms in his cases to the rise in pulmonary blood pressure caused by the narrowing of the main branches, but this is unlikely, as it has been shown that tying the artery to one lung causes little or no permanent rise in the pulmonary arterial pressure. It seems more likely that both in the patients with and in those without patency of the ductus or some other congenital cardiac abnormality, the cause of the aneurysm is weakness (probably congenital) of the wall of the artery, though this was proved only in Esser's case, in which the wall of the aneurysm was extremely thin and deficient in elastic tissue.

4. *Syphilitic Aneurysm*.—Reports of 11 cases have been collected from the recent literature.^v Nine of the patients were men and 2 women, and the ages ranged from 32 to 58 (average, 48). There was no clinical evidence of syphilis in 3 of these, though the changes noted post mortem were characteristic.

In 1 case²⁵ there were no circulatory symptoms, and the patient died of progressive dementia. Occasionally^w repeated hemoptysis was the first symptom, but in most cases the symptoms were merely those of progressive congestive heart failure. In some there was little cyanosis; in others it was so marked that a diagnosis of congenital cardiac disease was made.²³⁶ There was no evidence of mediastinal pressure in

(v) 9 (2 cases), 25, 166, 170, 236 (2 cases), 238, 278, 311.

(w) 166, 311.

any case. The heart was usually enlarged to the right and left. Often there were no abnormalities on auscultation, or only mitral and basal systolic murmurs, but the pulmonary second sound was sometimes accentuated, and in some cases there were diastolic murmurs to the left of the sternum.^x

The roentgenograms (taken in 4 cases) showed an enlarged heart and a bulging pulmonary artery. The electrocardiogram (in 2 cases) showed preponderance of the right ventricle. The diagnosis was made (on the basis of the roentgenographic evidence) before death in only 1 case.¹⁶⁶

Death was usually due to congestive heart failure. In 2 cases it was sudden owing to occlusion of the pulmonary artery by a thrombus¹⁷⁰ and to rupture of a dissecting aneurysm into the pericardium.²³⁶

At autopsy the heart was always enlarged usually owing to hypertrophy of the right ventricle, occasionally with the left ventricle smaller than normal.²³⁸ At times³¹¹ the left ventricle also was enlarged. Sometimes aortic syphilis with aneurysm or aortic incompetence also was present.^y

In 4 cases the aneurysm was confined to the stem of the pulmonary artery. In 2 it was fusiform and in 2 saccular. In the others there was aneurysm of one or the other main artery, either with or without involvement of the stem also. The sacs were usually partly or completely occluded by thrombi. Typical microscopic changes of syphilitic mesarteritis were present in all cases in which sufficient details were given, and in 1 case³¹¹ spirochetes were found in the wall.

DISSECTING ANEURYSMS

Reports of 4 cases have been found in the literature, but the much quoted case of Brown⁴⁶ may be dismissed, as the rupture was in the aorta and the effused blood merely spread along the adventitia of the pulmonary artery. Arrillaga's⁹ case is also doubtful, as it is merely stated that a somewhat dilated pulmonary artery had burst into the pericardium. The 2 other cases were in a man of 33⁹⁰ and a woman of 28.²³⁶ In the first patient, about two weeks before death, there was severe pain in the chest. He returned to work for one day and died in his sleep the same night. The second patient had been told at the age of 12 that she had cardiac disease. She was admitted to the hospital with acute nephritis. The heart was enlarged, and there was a systolic and diastolic murmur in the pulmonary area. She suddenly collapsed and died eight days after admission. At autopsy in both cases the pericardium was found to be full of blood. The right ventricle

(x) 9, 166, 311.

(y) 236, 238, 311.

was hypertrophied. In the first case there was a patent ductus arteriosus. At the bifurcation of the stem of the pulmonary artery the intima and media were torn through, and a dissecting aneurysm had formed and burst into the pericardium. In the second case there were changes that were grossly and microscopically characteristic of syphilis of both main pulmonary arteries. In the stem there was a right angle tear through the intima 2 cm. above the cusps. A dissecting aneurysm had formed from this and had burst into the pericardium.

Dissecting aneurysms of the pulmonary arteries thus appear to be even rarer than those of the aorta. In the 2 cases mentioned they were associated with patency of the ductus arteriosus and syphilitic arteritis, respectively. Dissecting aneurysms of the aorta occur rarely in association with syphilitic aortitis. No report of a case of dissecting aneurysm of the aorta associated with patent ductus arteriosus has been found in the literature. The common cause appears to be a peculiar form of degeneration of the aortic media. This was not described in either of the 2 cases of dissecting aneurysm of the pulmonary artery previously mentioned, but Neuberger,²¹⁹ in a case of dissecting aneurysm of the aorta with the characteristic degeneration of the media, observed similar but slighter changes in the unruptured pulmonary artery.

SUMMARY AND CONCLUSIONS

This lengthy survey seems to show that the pulmonary circulation plays an important part both in the physiology and in the pathology of the circulation as a whole, but that this part is, with rare exceptions, passive rather than active. The structure of the pulmonary vessels is such that they cannot be expected to play an important part in the regulation of the circulation through the lungs. The experimental evidence on this point is conflicting as to the nature (if any) of the response of the pulmonary vessels to most forms of nervous and pharmacologic stimuli, and it seems probable that any such responses must be feeble and of little importance in regulating the flow of blood through the lungs. By far the most important influence in regulating the pulmonary circulation is the activity of the heart and particularly the state of balance between the two sides of the heart, an increased output of the right side or a diminished output of the left causing congestion of the lungs and vice versa. Two of the most important symptoms of congestive heart failure, namely dyspnea and cyanosis, are dependent on congestion of the lungs caused in this way. There is no evidence that vasomotor activity of the pulmonary vessels is able to modify the process in any way. Again, the pulmonary circulation has so great a reserve (provided by the ready distensibility of the small pulmonary vessels and the large number of "reserve capillaries" through which blood does not

ordinarily flow) that it is difficult to embarrass it by occluding large branches of the pulmonary artery. Ligature of the artery to one lung causes only slight and transient increase in the pressure in the right ventricle, and the cross-sectional area of the stem of the pulmonary artery must be diminished by 75 per cent before the systemic blood pressure falls and by 90 per cent before death occurs (in acute experiments). No doubt even greater degrees of narrowing could be borne if brought about gradually. This is important evidence against the view, so frequently expressed, that comparatively minor degrees of pulmonary arterial disease are the cause of important changes in the heart and of grave symptoms ultimately resulting in death.

Practically all the varieties of vascular disease occurring in the systemic circulation may be observed also in the pulmonary circulation. Some forms, such as syphilitic arteritis, are less common, and others, such as septic and tuberculous arteritis, are more common than in the systemic circulation. Atherosclerosis is exceedingly common, having been noted microscopically in some degree in 97 per cent of 100 consecutive unselected autopsies. Its incidence is therefore as great, though its degree is not so marked, as in the systemic circulation. Its very frequency makes it difficult to determine etiologic factors, though its severity increases somewhat with age and with conditions thought to be associated with a raised pulmonary arterial pressure, such as cardiac disease or chronic pulmonary disease. These are evidently not the only factors, however, since atherosclerosis, sometimes marked, may occur in young persons with no chronic cardiac or pulmonary disease. Moreover, in chronic disease of the lungs, in which it might be expected that though the pulmonary artery pressure would be raised the pulmonary venous pressure would be lowered, marked venous sclerosis may occur. Again, no constant relationship is found between the thickness of the right ventricle and the degree of pulmonary atherosclerosis. There is no good evidence that even the most marked pulmonary atherosclerosis plays an important part in the production of symptoms in these cases.

A few cases of primary pulmonary arteriosclerosis have been reported in the literature, and 2 further cases have been described. This is a condition in which marked pulmonary arterial lesions of several histologic types are associated with hypertrophy of the right ventricle and ultimately heart failure in the absence of the usual causes of heart failure. It is usually said that the arterial lesions are primary and that the hypertrophy of the right side of the heart and the heart failure are secondary, but for the reasons previously given it is concluded that the vascular lesions are rarely extensive enough in themselves to embarrass the pulmonary circulation seriously and that more probably

they and the hypertrophy of the right side of the heart are manifestations of some common unknown cause.

The concept of Ayerza's disease has in the past dominated the consideration of pulmonary vascular disease. It is shown that this concept has varied continuously since its origination, and that the cases of Ayerza's disease that have been described are indistinguishable from cases of failure of the right side of the heart secondary to chronic pulmonary disease and are associated with fairly marked pulmonary atherosclerosis. There seems to be nothing to be gained by retaining the term.

Thrombi, whether embolic or formed in situ, are common in the pulmonary circulation, being found in 28 of 100 consecutive unselected autopsies. They ultimately become completely organized. They rarely cause symptoms unless a large branch of the pulmonary artery is suddenly blocked. The lungs appear to form a filter in the course of the circulation in which solid particles of clot, tumor, fat and other substances are trapped and prevented from entering the systemic circulation.

BIBLIOGRAPHY

1. Abbott, M., in *Nelson Loose-Leaf Medicine*, New York, Thomas Nelson & Sons, 1931.
2. Achard, C.: *Cardiaques noirs et artérites pulmonaires*, Bull. méd., Paris **44**:409, 1930.
3. Alexander, H. L.; Luten, D., and Kountz, W. B.: The Effects on the Heart of Long-Standing Bronchial Asthma, *J. A. M. A.* **88**:882 (March 19) 1927.
4. Allbutt, T. Clifford: *Arteriosclerosis*, New York, The Macmillan Company, 1925.
5. Andral (1829), quoted by Costa.⁶³
6. Anitschkow, N.: *Experimental Arteriosclerosis in Animals*, in Cowdry, E. V.: *Arteriosclerosis*, New York, The Macmillan Company, 1933, p. 271.
7. Anrep, G. V., and Bulatoa, E.: *Observations on the Pulmonary Circulation*, *J. Physiol.* **40**:175, 1925.
8. Arrillaga, F. C.: *Sclerose de l'artère pulmonaire secondaire à des états pulmonaires chroniques*, *Arch. d. mal. du coeur* **6**:518, 1913.
9. —Sclerose de l'artère pulmonaire, *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:292, 1924.
10. —Anévrismes de l'artère pulmonaire, *ibid.* **48**:1230, 1924.
11. —La arteritis pulmonar y su cuadro clinico, Buenos Aires, 1925; quoted by Durand.⁸⁸
12. —and Elizalde, P. J.: *Caractères histopathologiques de la maladie de Ayerza*, *Compt. rend. Soc. de biol.* **84**:161, 1921.
13. Aschoff, L.: *Lectures on Pathology*, New York, Paul B. Hoeber, Inc., 1924, p. 131.
14. —in Cowdry, E. V.: *Arteriosclerosis*, New York, The Macmillan Company, 1933, p. 1.

15. Atkins, H. J. B.: Ayerza's Disease, *Guy's Hosp. Rep.* **82**:480, 1932.
16. Aubertin, C.; Lévy, R., and Foulon, P.: Disparition rapide de la cyanose, du souffle tricuspidien, et des oedèmes chez un cardiaque noir à la suite d'une abondante hémorrhagie interne, *Presse méd.* **36**:433, 1928.
17. Aust, C.: Casuistischer Beitrag zur Sklerose der Lungenarterie, *München. med. Wchnschr.* **39**:689, 1892.
18. Averbuck, S. H.: Differentiation of Acute Coronary Artery Thrombosis from Pulmonary Embolization, *Am. J. M. Sc.* **187**:391, 1934.
19. Bacon, C. M., and Apfelbach, C. W.: Primary Sclerosis of the Pulmonary Artery and Its Branches, *Tr. Chicago Path. Soc.* **12**:293, 1927.
20. ———Primary Sclerosis of the Pulmonary Artery and Its Branches, *Arch. Path. & Lab. Med.* **3**:80 (May) 1927.
21. Barker, N. W.: Polycythemia Vera and Chronic Pulmonary Disease, *Arch. Int. Med.* **47**:94 (Jan.) 1931.
22. Barlaro, quoted by Brachetto-Brian.⁴⁰
23. Barnes, A. R., and Whitten, M. B.: Study of T Wave Negativity in Predominant Ventricular Strain, *Am. Heart J.* **5**:14, 1929.
24. ———and Yater, W. M.: Failure of the Right Ventricle Due to an Ancient Thrombus in the Pulmonary Artery, *M. Clin. North America* **12**:1610, 1929.
25. Barth, H.: Ein Fall von Mesarteriitis luetica der Arteria pulmonalis mit Aneurysmabildung, *Frankfurt. Ztschr. f. Path.* **5**:139, 1910.
26. Bell, E. T.: Arteriosclerosis of the Abdominal Viscera and Extremities, in Cowdry, E. V.: *Arteriosclerosis*, New York, The Macmillan Company, 1933, p. 473.
27. Benda, C., in Aschoff, L.: *Pathologische Anatomie*, Jena, Gustav Fischer, 1923.
28. ———Venen, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1924, vol. 2.
29. Berry, J. L.; Brailsford, J. F., and Daly, I. de B.: The Bronchial Vascular System in the Dog, *ibid.* **109**:214, 1931.
30. ———and Brenner, O.: Unpublished observations.
31. ———and Daly, I. de B.: The Relation Between the Pulmonary and Bronchial Vascular Systems, *Proc. Roy. Soc., London, s.B* **109**:319, 1931.
32. Billings, F. T.: Primary Thrombosis of the Pulmonary Artery, *Pennsylvania M. J.* **25**:151, 1921.
33. Blechman, G., and Paulin, A.: Anévrisme de l'artère pulmonaire par endocardite aigüe greffée sur une cardiopathie congénitale chez un enfant, *Arch. d. mal. du coeur* **15**:472, 1922.
34. Boas, E. P., and Mann, H.: The Right Ventricle in Pulmonary Tuberculosis, *Arch. Int. Med.* **28**:62 (July) 1921.
35. Boldero, H. E. A., and Bedford, D. E.: Infective Endocarditis in Congenital Heart Disease Involving the Pulmonary Artery, *Lancet* **2**:747, 1924.
36. Bordet, E.: L' image du coeur dans la sclérose de l'artère pulmonaire, *Paris méd.* **2**:20, 1927.
37. Borelli, L.: Sopra un caso di arteriosclerosis polmonare, *Gior. d. r. Accad. di med. di Torino* **19**:84, 1913; quoted by Durand.⁸⁸
38. Borst, M.: Pathologisch-anatomische Beobachtungen zur spanischen Grippe, *München. med. Wchnschr.* **65**:1342, 1918.
39. Boswell, C. H., and Palmer, H. D.: Progressive Thrombosis of the Pulmonary Artery, *Arch. Int. Med.* **47**:799 (May) 1931.

40. Brachetto-Brian, D.: Concepto anatomo-patologico de los cardiacos negros de Ayerza, *Rev. Soc. de med. int. y Soc. de fisiol.* **6**:821, 1925.
41. Bramwell, C.: The Physical Properties of Arteries in Health and Disease, in Cowdry, E. V.: *Arteriosclerosis*, New York, The Macmillan Company, 1933, p. 77.
42. Bredt, H.: Die primäre Erkrankung der Lungenschlagader in ihren verschiedenen Formen, *Virchows Arch. f. path. Anat.* **284**:126, 1932.
43. Brenner, O.: Sclerosis of the Pulmonary Artery with Thrombosis, *Lancet* **1**:911, 1931.
44. Brisson (1803), quoted by Ljungdahl.
45. Brooks, Harlow: A Case of Arteriosclerosis of the Pulmonary Vessels, *Proc. New York Path. Soc.* **7**:177, 1907-1908.
46. Brown, Lawrason: Dissecting Aneurysm of the Aorta and Pulmonary Artery Following Rupture of the Arch of the Aorta, *New York M. J.* **88**:1, 1908.
47. Bruce, J. D.; Wilson, F. N.; Hickey, P. M.; Collier, F. A., and Warthin, A. S.: Ayerza's Disease with Atherosclerosis and Syphilis of the Pulmonary Arteries, *Ann. Clin. Med.* **5**:9, 1926.
48. Brüning, H.: Untersuchungen über das Vorkommen der Angiosklerose im Lungenkreislauf, *Beitr. z. path. Anat. u. z. allg. Path.* **30**:457, 1901.
49. Bryant, J. H.: Functional Pulmonary Incompetence and Dilatation and Atheroma of the Pulmonary Arteries as Complications of Mitral Stenosis, *Guy's Hosp. Rep.* **55**:83, 1901.
50. —and Hale-White, W.: A Case of Calcification of the Arteries and Obliterative Endarteritis Associated with Hydronephrosis in a Child Aged 6 Months, *ibid.* **55**:17, 1901.
51. Campbell, J. A.: Further Observations on Oxygen Acclimatisation, *J. Physiol.* **63**:325, 1927.
52. Caussade, G., and Tardieu, A.: L'infection secondaire subaigüe et prolongée du poumon cardiaque, *Rev. de méd., Paris* **43**:977, 1926.
53. —Artérite pulmonaire syphilitique chez un cardiaque noir, *Bull. et mém. Soc. méd. d. hôp. de Paris* **52**:871, 1928.
54. Cheney, G.: Ayerza's Disease with a Report of Two Cases, *Am. J. M. Sc.* **174**:34, 1927.
55. Chiari, H.: Ueber Veränderungen in der Arteria pulmonalis in Fällen von akuter rheumatischer Endocarditis oder bei Herzfehlern rheumatischen Ursprungs, *Klin. Wchnschr.* **9**:1862, 1930.
56. Chvostek, F.: Asthma cardiale und Stenokardie, *Wien. klin. Wchnschr.* **34**:519, 1921.
57. Clarke, R. C.; Coombs, C. F.; Hadfield, G., and Todd, A. T.: On Certain Abnormalities, Congenital and Acquired, of the Pulmonary Artery, *Quart. J. Med.* **21**:51, 1927.
58. Clarkson, S., and Newburgh, L. H.: The Relation Between Atherosclerosis and Ingested Cholesterol in the Rabbit, *J. Exper. Med.* **43**:595, 1926.
59. Clerc, M. A., and Deschamps, N.: *Coeur et vaisseaux*, in *Précis de pathologie médicale*, Paris, Masson & Cie, 1931, vol. 4.
60. —Bascounet, M., and Froyez, R.: Communication entre l'aorte et l'artère pulmonaire avec survie de quatre ans, *Bull. et mém. Soc. méd. d. hôp. de Paris* **47**:1288, 1931.
61. Corten, M. H.: Ueber Wesen und Bedeutung der Veränderungen der Lungengefäße bei der Grippepneumonie, *Virchows Arch. f. path. Anat.* **280**:463, 1931.

62. Coryllos, P. N., and Birnbaum, G. L.: The Circulation in the Compressed, Atelectatic and Pneumonic Lung, *Arch. Surg.* **19**:1346 (Dec.) 1929.
63. Costa, A.: Sulla frequenza, distribuzione e genesis dell' arteriosclerosi nel tronco dell' arteria polmonare in base a ricerche istopatologiche sistematiche, *Clin. med. ital.* **58**:325, 1927.
64. —Nuove ricerche sistematiche sull' arteriosclerosi dell' arteria polmonare con riferimenti alla sclerosi primitiva e alla malattia di Ayerza, *ibid.* **59**:193, 1928.
65. Cowdry, E. V.: The Structure and Physiology of the Blood Vessels, in Cowdry, E. V.: *Arteriosclerosis*, New York, The Macmillan Company, 1933, p. 53.
66. Crouzon and Grenadier: *Bull. et mém. Soc. méd. d. hôp. de Paris* **46**:34, 1922.
67. Crudeli, C. T.: *Riv. clin. di Bologna* **7**:37, 1868; quoted by Romberg.
68. Daly, I. de B.: The Influence of Mechanical Conditions of the Circulation on the Electrocardiogram, *Proc. Roy. Soc., London, s.B* **95**:279, 1923-1924.
69. —The Effect of Alterations in the Peripheral Resistance and in the Capacity of the Circulation, *ibid.* **99**:306, 1926.
70. —The Conditions Governing the Blood Capacity of the Lungs, *J. Physiol.* **65**:422, 1928.
71. —The Resistance of the Pulmonary Vascular Bed, *ibid.* **69**:238, 1930.
72. —Reactions of the Pulmonary and Bronchial Blood Vessels, *Physiol. Rev.* **13**:149, 1933.
73. —and von Euler, U.: The Functional Activities of the Vasomotor Nerves to the Lungs of the Dog, *Proc. Roy. Soc., London, s.B* **110**:92, 1932.
74. Darré, H., and Albot, G.: Une forme de syphilis du poumon; sclérose syphilitique nodulaire, avec panartérite pulmonaire, *Ann. d'anat. path.* **4**:861, 1927.
75. Desclin, L.: Ueber chronische Thrombosen des Hauptstammes und der Hauptäste der Arteria pulmonalis, *Frankfurt. Ztschr. f. Path.* **40**:161, 1930.
76. —and Regnier, M.: La thrombose chronique du tronc et des branches principales de l'artère pulmonaire, *Arch. d. mal. du coeur* **24**:726, 1931.
77. Dietrich (1850), quoted by Costa.⁶³
78. Dietrich, E.: Beitrag zur Diagnostik der Pulmonalsklerose, *Fortschr. a. d. geb. d. Röntgenstrahlen* **36**:990, 1927.
79. Dioniso: *Cong. di path., Palermo*, 1908; quoted by Durand.⁸⁸
80. Dixon, W. E., and Hoyle, J. C.: Studies in the Pulmonary Circulation, *J. Physiol.* **70**:1, 1930.
81. Drinker, C. K.; Churchill, E. D., and Ferry, R. M.: The Volume of Blood in the Heart and Lungs, *Am. J. Physiol.* **77**:590, 1926.
82. —Peabody, F. W., and Blumgart, H. L.: The Effect of Pulmonary Congestion on the Ventilation of the Lungs, *J. Exper. Med.* **35**:77, 1922.
83. Dubrow, J. L.: The Effect of Permanent Pulmonary Collapse on the Heart, *J. A. M. A.* **90**:1364 (April 28) 1928.
84. Ducach, J.: Ein Fall von Sklerose der Arteria pulmonalis (Morbus Ayerza-Arrillaga), *Ztschr. f. klin. Med.* **10**:313, 1928.
85. Dunn, J. S.: Measurement of the Pressure Changes in the Right Ventricle by Cardiac Puncture, *Quart. J. Med.* **13**:46, 1919.
86. —The Effect of Experimental Pleural Effusion on Pressure Changes in the Right Ventricle, *ibid.* **13**:57, 1919.

87. —The Effects of Multiple Embolism of the Pulmonary Arterioles, *ibid.* **13**:129, 1919.
88. Durand, P.: Endoartérite oblitérante primitive de l'artère pulmonaire (sclérose primitive), Thèse de Paris, no. 67, Paris, 1927.
89. Durante, G.: Athérome congénital de l'aorte et de l'artère pulmonaire, *Bull. et mém. Soc. méd. d. hôp. de Paris* **1**:97, 1899.
90. Durno, L., and Langdon Brown, W.: A Case of Dissecting Aneurysm of the Pulmonary Artery; Patent Ductus Arteriosus; Rupture into the Pericardium, *Lancet* **1**:1693, 1908.
91. Edeiken, J.: The Effect of Spinal Deformities on the Heart, *Am. J. M. Sc.* **186**:99, 1933.
92. Ehlers, H. W. E.: Zur Histologie der Arteriosklerose der Pulmonalarterie, *Virchows Arch. f. path. Anat.* **178**:427, 1904.
93. Elias, H., and Feller, A.: Ueber verschiedene Stauungstypen, *Wien. klin. Wchnschr.* **38**:725, 1925.
94. Eliaszewitz, P. A.: Ueber ungewöhnliche Lungenarterien und Herzveränderungen bei Mitralstenose, *Virchows Arch. f. path. Anat.* **279**:436, 1930.
95. Ellis, L. B., and Weiss, S.: The Measurement of Capillary Pressure, *J. Clin. Investigation* **8**:47, 1929.
96. Engelhard, P.: Sklerosen im Gebiet der Arteria pulmonalis, *Deutsche med. Wchnschr.* **40**:1015, 1923.
97. —Der Wert der Spirometrie für die Klinik der Herzkrankheiten mit Lung-
enstauung, und ihr Ausbau zu einer Funktionsprüfung, *Deutsches Arch. f. klin. Med.* **156**:1, 1927.
98. Eppinger, H., and Wagner, R.: Zur Pathologie der Lunge, *Wien. Arch. f. inn. Med.* **1**:83, 1920.
99. Eschbach, H.: Ueber ein malignes Leiomyom des Endocards mit Verstopfung
der Lungenschlagader, *Beitr. z. path. Anat. u. z. allg. Path.* **80**:672, 1928.
100. Escudero, P.: Les cardiaques noirs et la maladie de Ayerza, *Arch. d. mal. du coeur* **19**:439, 1926.
101. Esser, A.: Seltene Formen von Aneurysmen, *Ztschr. f. Kreislaufforsch.* **24**:737, 1932.
102. Evans, F. A.: Unilateral Sclerosis of the Pulmonary Artery, *Bull. Johns Hopkins Hosp.* **24**:284, 1913.
103. Fischer, W.: Ueber die Sklerose der Lungenschlagader und ihre Entstehung, *Deutsches Arch. f. klin. Med.* **97**:230, 1909.
104. Förster, E.: Ein Fall von obturierenden Thrombus im rechten Ast der Pul-
monalis, und isolierte Trikuspidalinsuffizienz, *Wien. med. Wchnschr.* **72**:
617, 1922.
105. Franklin, K. J.: The Actions of Adrenalin and Acetyl Choline on the Iso-
lated Pulmonary Vessels and Azygos Vein of the Dog, *J. Physiol.* **75**:
471, 1932.
106. Frey: Das klinischen Bild der primären Sklerose der Pulmonalarterien,
München. med. Wchnschr. **69**:1742, 1922.
107. Fried, B. M.: Primary Carcinoma of the Lung, *Medicine* **10**:373, 1932.
108. Frothingham, C.: A Case of Extensive Spontaneous Thrombosis of the
Small Branches of the Pulmonary Artery, *Tr. A. Am. Physicians* **42**:70,
1927.
109. —A Case of Extensive Bilateral Thrombosis of the Smaller Branches of
the Pulmonary Arteries, *Am. J. Path.* **5**:11, 1929.
110. Fürth, K., and Weber, F. P.: A Case of Malignant Pulmonary Endarteritis
After Gonorrhoea, *Edinburgh M. J.* **18**:33, 1905.

111. Gaddum, J. H., and Holtz, P.: The Localisation of the Action of Drugs on the Pulmonary Vessels of Cats and Dogs, *J. Physiol.* **77**:139, 1933.
112. Gibbon, G. H.; Hopkinson, M., and Churchill, E. D.: Changes in the Circulation Produced by Gradual Occlusion of the Pulmonary Artery, *J. Clin. Investigation* **11**:543, 1932.
113. Giroux, L.: Sclérose et athérome de l'artère pulmonaire: Rôle des conditions mécaniques, *Arch. d. mal. du coeur* **3**:218, 1910.
114. —Sclérose et athérome de l'artère pulmonaire, Thèse de Paris, no. 149, 1910.
115. von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, *Am. J. Path.* **2**:235, 1926.
116. Glynn, E., and Knowles, R. E.: Some Observations on Fatal Cases of Pulmonary Thrombosis, *Brit. M. J.* **2**:1412, 1910.
117. Goedel, A.: Zur Kenntnis der Hypertrophie des rechten Herzens und schwerer Kreislaufstörung infolge Verödung der Lungenschlagaderperipherie, *Virchows Arch. f. path. Anat.* **277**:507, 1930.
118. Gordon, H., and Perla, D.: Subacute Bacterial Endarteritis of the Pulmonary Artery Associated with Patent Ductus Arteriosus and Pulmonary Stenosis, *Am. J. Dis. Child.* **41**:98 (Jan.) 1931.
119. Gouley, B. A., and Eimon, J.: The Pathology of Rheumatic Pneumonia, *Am. J. M. Sc.* **183**:359, 1932.
120. Gray, S. H., and Aitken, L.: Late Gross Lesions in the Aorta and Pulmonary Artery Following Rheumatic Fever, *Arch. Path.* **8**:451 (Sept.) 1929.
121. Gross, L., and Kugel, M. A.: Topographic Anatomy and Histology of the Valves in the Human Heart, *Am. J. Path.* **7**:445, 1931.
122. Gross, P.: Tuberculous Vegetations of the Trunk of the Pulmonary Artery, *Am. J. Path.* **9**:17, 1933.
123. Hall, F. de H.: Haemoptysis Due to High Tension, *Lancet* **2**:329, 1915.
124. Handford, H.: A Case of Gummata of the Heart, *Brit. M. J.* **2**:1745, 1904.
125. Hare, D. C., and Ross, J. M.: Syphilitic Disease of the Pulmonary Artery, with an Account of a Case, *Lancet* **2**:806, 1929.
126. Harris, I.: Vascular Disease and the Sympathetic System, *Brit. M. J.* **1**:789, 1927.
127. Harrison, T. R.; Calhoun, J. A.; Cullen, G. E.; Wilkins, W. E., and Pilcher, C.: Reflex Versus Chemical Factors in the Production of Rapid Breathing, *J. Clin. Investigation* **11**:132, 1932.
128. —Harrison, W. G.; Calhoun, J. A., and Marsh, J. P.: Congestive Heart Failure: The Mechanism of Dyspnea on Exertion, *Arch. Int. Med.* **50**:690 (Nov.) 1932.
129. Harrison, W. F.: Congenital Heart Disease (Tetralogy of Fallot); Collateral Pulmonary Circulation; Massive Right Sided Endocarditis, *Am. Heart J.* **5**:213, 1929.
130. Hart, C.: Ueber die Embolie der Lungenarterie, *Deutsches Arch. f. klin. Med.* **84**:449, 1905.
131. —Ueber die isolierte Sklerose der Pulmonalarterie, *Berl. klin. Wchnschr.* **53**:304, 1916.
132. Heymans, C.; Bouckaert, J. J., and Regniers, P.: Le sinus carotidien et la zone homologue cardio-aortique, Paris, Gaston Doin & Cie, 1933.
133. Hochrein, M., and Keller, C. J.: Die nervöse Regulation der Durchblutung und Blutfüllung der Lunge, *Arch. f. exper. Path. u. Pharmacol.* **166**:229, 1932.

134. Holman, E., and Beck, C. S.: The Physiological Response of the Circulatory System to Experimental Alterations; the Effect of Aortic and Pulmonary Stenoses, *J. Clin. Investigation* **3**:283, 1926.
135. Holtz, P.: The Action of Pituitary Posterior Lobe Extract on Different Parts of the Circulatory System, *J. Physiol.* **76**:149, 1932.
136. Hornowski, J.: Untersuchungen über Atherosklerose, *Virchows Arch. f. path. Anat.* **215**:280, 1914.
137. Jacquet: *Semaine méd.* **28**:437, 1908.
138. Jores, L.: Arterien, in Hencke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1924, vol. 2.
139. Jump, H. D., and Baumann, A.: Large Thrombus of the Pulmonary Artery with Chronic Cyanosis and Polycythaemia, *Pennsylvania M. J.* **32**:754, 1929.
140. Kaplan, S.: Zur Kenntnis der primären Geschwülste des Herzens und seiner grossen Gefässe, *Ztschr. f. Kreislaufforsch.* **24**:565, 1932.
141. Karsner, H. T.: Productive-Cicatricial Syphilitic Disease of the Pulmonary Artery, *Arch. Int. Med.* **51**:367 (March) 1933.
142. —Sclerosis of the Pulmonary Arteries, in Cowdry, E. V.: *Arteriosclerosis*, New York, The Macmillan Company, 1933.
143. —and Ash, J. E.: Experimental Bland Infarction of the Lung, *J. M. Research* **22**:205, 1912-1913.
144. Katz, L. N., and Siegel, M. L.: The Importance of the Variable Capacity of the Aorta in Averting Back Pressure in the Right Heart and Pulmonary Artery, *Am. J. Physiol.* **89**:417, 1929.
145. —and Wiggers, C. J.: The Influence of a High Systemic Pressure on the Right Ventricle and Pulmonary Circulation, *ibid.* **82**:91, 1927.
146. Kidd, P.: Diffuse Endarteritis of the Pulmonary Vascular System, *Tr. Path. Soc. London* **36**:218, 1903.
147. Kisch, E.: Das Verhalten von Herz und Kreislauf bei rechtsseitiger (pulmonaler) Herzhypertrophie, *Würzb. Abhandl. a. d. Gesamtgeb. d. prakt. Med.* **22**:73, 1925.
148. Kitamura, S.: Ueber die Sklerose der Pulmonalarterie bei fortgesetztem übermässigem Biergenuss, *Ztschr. f. klin. Med.* **65**:14, 1908.
149. Klob: *Wien. Wchnbl.* **21**:45, 1865; quoted by Romberg.²⁵⁵
150. Konstam, G. L. S.: Syphilis of the Lung with Pulmonary Arteritis (Ayerza's Disease), *Lancet* **2**:756, 1929.
151. Krutsch, G.: Ueber rechtsseitige Herzhypertrophie durch Einengung des Gesamtquerschnittes der kleineren und kleinsten Lungenarterien, *Frankfurt. Ztschr. f. Path.* **23**:163, 1920.
152. Kugel, M. A., and Epstein, E.: Lesions in the Pulmonary Artery and Valve Associated with Rheumatic Heart Disease, *Arch. Path.* **6**:247 (Aug.) 1928.
153. Kuntschik: Zur Kenntnis der sogenannten primären Pulmonalsklerose, *Ztschr. f. Kreislaufforsch.* **23**:183, 1931.
154. Kux, E.: Myocarditis gummosa und Mesopulmonitis luica, *Ztschr. f. Kreislaufforsch.* **24**:1, 1924.
155. Laignel-Lavastine, Coulaud and Largeaue: Scléroderme aigüe, *Bull. et mém. Soc. méd. d. hôp. de Paris* **46**:1586, 1922.
156. Landsberg, F.: Ueber den syphilitischen Pulmo lobatus, *Virchows Arch. f. path. Anat.* **277**:583, 1930.

157. Lange, G.: Zur Frage der Thromboarteriolitis pulmonum, *Deutsches Arch. f. klin. Med.* **143**:359, 1924.
158. Laubry, C., in discussion on Ribierre and Giroux.²⁵⁰
159. —Chaperon, R., and Thomas, M.: Etudes radiologiques du hile et des vaisseaux pulmonaires a l'état normal et pathologique, *Ann. de méd.* **20**: 217, 1926.
160. —Huguenin, R., and Thomas, M.: Classification anatomoclinique des artérites pulmonaires, *Ann. d'anat. path.* **4**:595, 1927.
161. —and Parvu, M.: Artériosclérose généralisée de l'artère pulmonaire, *Bull. et mém. Soc. méd. d. hôp. de Paris* **27**:1320, 1909.
162. —Lésion complexe de l'artère pulmonaire d'origine congénitale, *ibid.* **44**: 1395, 1920.
163. —and Routier, D.: Insuffisance aiguë du coeur droit par compression du tronc de l'artère pulmonaire, *ibid.* **46**:636, 1922.
164. —Un cas d'insuffisance ventriculaire droite par compression de l'artère pulmonaire; anévrisme artério-veineux carotido-jugulaire gauche, *ibid.* **46**:700, 1922.
165. —and Thomas, M.: Les lésions de l'artère pulmonaire et leurs conséquences au cours du rétrécissement mitral, *ibid.* **50**:639, 1926.
166. —Les formes anatomocliniques des artérites pulmonaires chez les syphilitiques, *ibid.* **51**:9, 1927.
167. —Sur les artérites pulmonaires, *ibid.* **52**:881, 1928.
168. Leconte, M., and Bordet, E.: Dilatation anévrismatique de l'artère pulmonaire, *ibid.* **48**:353, 1924.
169. Lenoble, Hallier, Pineau and Pouzin: Sclérose de l'artère pulmonaire, *Arch. d. mal. du coeur* **20**:246, 1927.
170. Letulle, M., and Jaquelin, A.: Anévrisme syphilitique de l'artère pulmonaire, *Arch. d. mal. du coeur* **13**:385, 1920.
171. Lewis, T.: *Diseases of the Heart*, New York, The Macmillan Company, 1933.
172. —and Landis, E.: Further Observations upon a Variety of Raynaud's Disease, with Special Reference to Scleroderma and to Arteriolar Defects, *Heart* **15**:329, 1931.
173. Liebig, H.: Ueber die primäre Pulmonalsklerose, *Zentralbl. f. Herz- u. Gefässkr.* **18**:45, 1926.
174. Linden, W.: Isolierte Pulmonalsklerose im jüngsten Kindesalter, *Virchows Arch. f. path. Anat.* **252**:229, 1924.
175. Lissauer, M.: Ueber das Aneurysma am Stamme der Pulmonalarterie, *Virchows Arch. f. path. Anat.* **180**:462, 1905.
176. Ljungdahl, M.: Untersuchungen über die Arteriosklerose des kleinen Kreislaufs, Wiesbaden, J. F. Bergmann, 1915.
177. —Gibt es eine chronische Embolisierung der Lungenarterie? *Deutsches Arch. f. klin. Med.* **160**:1, 1928.
178. Lobstein (1835), quoted by Costa.⁶³
179. Löwenstein, K.: Ueber Thromboarteriitis pulmonalis, *Frankfurt. Ztschr. f. Path.* **27**:226, 1922.
180. Lucas, W. S.: Erythremia or Polycythemia with Chronic Cyanosis and Splenomegaly, *Arch. Int. Med.* **10**:597 (Dec.) 1912.
181. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis, *Medicine* **2**:1, 1923.
182. Lutembacher, R.: Syndrôme tricuspïdien terminal dans les lésions chroniques du poumon, *Arch. d. mal. du coeur* **9**:141, 1916.

183. —Endocardite subaiguë et endartérite pulmonaire chez les cardiaques, *ibid.* **10**:353, 1917.
184. —Erythrocyanose par thrombostase, *ibid.* **25**:630, 1932.
185. —Thrombose de la branche droite de l'artère pulmonaire, *ibid.* **26**:601, 1933.
186. Macaigne, M., and Nicaud, P.: Aspergillose primitive du poumon, avec artérite pulmonaire oblitérante, *Bull. et mém. Soc. méd. d. hôp. de Paris* **50**:183, 1926.
187. MacCallum, W. G.: Obliterative Pulmonary Arteriolosclerosis, *Bull. Johns Hopkins Hosp.* **49**:37, 1931.
188. —Acute and Chronic Infections as Etiological Factors in Arteriosclerosis, in Cowdry, E. V.: *Arteriosclerosis*, New York, The Macmillan Company, 1933, p. 355.
189. MacGregor, R. G.: Examination of the Pulmonary Circulation with the Microscope, *J. Physiol.* **80**:65, 1933.
190. MacMahon, H. E., and Weiss, S.: Carbon Tetrachloride Poisoning with Macroscopic Fat in the Pulmonary Artery, *Am. J. Path.* **5**:623, 1929.
191. Macnider, W.: The Production of Morbid Changes in the Blood Vessels of the Rabbit by Alcohol, *Arch. Int. Med.* **3**:175 (March) 1909.
192. MacPhedran and Mackenzie, J. J.: A Case of Massive Haemorrhagic Infarction of the Lung Due to Pulmonary Endarteritis and Thrombosis, *Tr. A. Am. Physicians* **18**:337, 1903.
193. Mair, W.: Atheroma of the Pulmonary Artery, *J. Path. & Bact.* **18**:127, 1913.
194. Marble, H. C., and White, P. D.: A Case of Traumatic Aneurysm of the Pulmonary Artery, *J. A. M. A.* **14**:1778 (June 26) 1920.
195. Mattiolo, G.: *Arch. per le sc. med.* **44**:174, 1921.
196. Mautner, H., and Pick, E. P.: Der Einfluss der Leber auf Blutdruck und Schlagvolumen, *Arch. f. exper. Path. u. Pharmakol.* **142**:271, 1929.
197. Maximow, A. A.: *Textbook of Histology*, Philadelphia, W. B. Saunders Company, 1930.
198. Meakins, J. C., and Davies, H. Whitridge: *Respiratory Function in Disease*, Edinburgh, Oliver & Boyd, 1925.
199. Means, J. H.: *Dyspnoea*, *Medicine* **3**:309, 1924.
200. —and Mallory, T. B.: Total Occlusion of the Right Branch of the Pulmonary Artery by an Organized Thrombus, *Ann. Int. Med.* **5**:417, 1931.
201. Mehlin, H.: Ueber akute mycotische Arteriitis der Pulmonalarterie, *Deutsches Arch. f. klin. Med.* **152**:257, 1926.
202. Meyer, O.: Zwei Fälle von Pulmonalsklerose, *München. med. Wchnschr.* **72**:1948, 1925.
203. Miller, H. R.: Sclerosis of the Pulmonary Artery and Its Branches, *M. Clin. North America* **9**:673, 1925.
204. Mobitz, W.: Die klinische Diagnose der schweren, durch isolierte primäre Arteriosklerose der Lungengefäße hervorgerufene Herzinsuffizienz, *Deutsches Arch. f. klin. Med.* **142**:115, 1923.
205. Modrakowski, G.: Durchströmungsgeschwindigkeit und Verhalten des Tonus der Gefäße und Bronchien an der überlebenden Katzenlunge, *Arch. f. d. ges. Physiol.* **158**:162, 1914.
206. —Ueber die experimentelle Erzeugung von Lungenwodem, *ibid.* **158**:527, 1914.
207. Möller, P.: Studien über embolische und autochthone Thromben in der Arteria pulmonalis, *Beitr. z. path. Anat. u. z. allg. Path.* **71**:27, 1922.

208. Mönckeberg, J. G.: Ueber die genuine Arteriosklerose der Lungenarterie, *Deutsche med. Wchnschr.* **33**:1243, 1907.
209. Moniz, E.; Carvalho, L. de, and Lima, A.: La visibilité des vaisseaux pulmonaires aux rayons X par injection dans l'oreillette droite de fortes solutions d'iodure de sodium, *Bull. Acad. de méd., Paris* **105**:627, 1931.
210. Moore, R. L., and Binger, C. A. L.: Observations on the Resistance to the Flow of Blood to and from the Lungs, *J. Exper. Med.* **45**:655, 1927.
211. Morse, P. F.: Symptomatic Polycythemia with Cyanosis and Dyspnea, *Arch. Int. Med.* **33**:459 (April) 1924.
212. Moschowitz, E.: Hypertension of the Pulmonary Circulation, *Am. J. M. Sc.* **174**:388, 1927.
213. —The Causes of Arteriosclerosis, *ibid.* **178**:244, 1929.
214. —The Pathogenesis of Brown Induration of the Lungs, *Am. Heart J.* **6**:171, 1930.
215. Münzer, E.: Gefäßsklerosen. Sklerosen der Arterien und Arteriolocapillaren im Gebiete der Aorta und Arteria pulmonalis, *Ergebn. d. ges. Med.* **4**:162, 1923.
216. Muscel, N.; Lazeanu, E., and Stoichitza, N.: Sur un cas d'anévrisme de l'artère pulmonaire, *Arch. d. mal. du coeur* **26**:140, 1933.
217. Nathan, M.: La maladie de Ayerza, *Presse méd.* **37**:773, 1927.
218. Neale, A. V., and Whitfield, A. G. W.: Rheumatism and Its Relation to Arterial Disease and Periarteritis nodosa, *Brit. M. J.* **2**:106, 1934.
219. Neuberger, K.: Ueber Aortenveränderungen bei Spontanruptur, *Ztschr. f. Kreislaufforsch.* **24**:169, 1932.
220. Obendorfer: Ueber die pathologische Anatomie der influenza-artigen Epidemie im Juli, 1918, *München. med. Wchnschr.* **65**:811, 1918.
221. Paine, C. G., and Platt, R.: Pulmonary Arteriosclerosis, *Brit. M. J.* **1**:698, 1931.
222. Pappenheimer, C. G., and von Glahn, W. C.: Lesions of the Aorta Associated with Acute Rheumatic Fever and with Chronic Heart Disease of Rheumatic Origin, *J. M. Research* **44**:489, 1924.
223. —A Case of Rheumatic Aortitis, with Early Lesions in the Media, *Am. J. Path.* **2**:15, 1926.
224. —Studies in the Pathology of Rheumatic Fever, *ibid.* **3**:583, 1927.
225. Parkinson, J., and Bedford, D. E.: The Pulmonary Artery Impression on the Oesophagus, *Lancet* **2**:337, 1931.
226. —and Clark-Kennedy, A. E.: Heart Failure with Normal Rhythm, *Quart. J. Med.* **19**:113, 1926.
227. —and Cookson, H.: The Size and Shape of the Heart in Goitre, *ibid.* **24**:499, 1931.
228. Patterson, S. W., and Starling, E. H.: On the Mechanical Factors Which Determine the Output of the Ventricles, *J. Physiol.* **48**:357, 1914.
229. Paul, J. R.: The Lesions in the Pulmonary Artery in Rheumatism, *Arch. Path.* **3**:354 (Feb.) 1927.
230. —Pleural and Pulmonary Lesions in Rheumatic Fever, *Medicine* **7**:383, 1928.
231. Peck, S. M.: The Pathologic Anatomy of Syphilis of the Pulmonary Artery, *Arch. Path.* **4**:365 (Sept.) 1927.
232. Perla, D., and Seligman, B.: Diffuse Obliterating Endarteritis of Unknown Etiology, *Arch. Path.* **7**:55 (Jan.) 1929.
233. Pezzi, C.: *Atti d. Soc. lomb. d. sc. Med. e biol.* **12**:60, 1922-1923; quoted by Durand.^{ss}

234. —and Silingardi, S.: Un cas d'ectase de l'artère pulmonaire avec insuffisance de l'appareil valvulaire, *Bull. et mém. Soc. méd. d. hôp. de Paris* **49**:117, 1925.
235. Pfister, E.: Ein Fall von obturierender Thrombosis im rechten Ast der Pulmonalis, *Wien. med. Wchnschr.* **72**:617, 1922.
236. Plenge, K.: Zur Frage der Syphilis der Lungenschlagader, *Virchows Arch. f. path. Anat.* **275**:572, 1930.
237. Plesch, J.: Arterial Atony and Arteriosclerosis, *Lancet* **1**:385, 1932.
238. Ploeger, A.: Das Aneurysma der Arteria pulmonalis, *Frankfurt. Ztschr. f. Path.* **4**:286, 1910.
239. Posselt, A.: Die klinische Diagnose der Pulmonalarteriensklerose, *München. med. Wchnschr.* **55**:1625, 1908.
240. —Die Erkrankungen der Lungenschlagader, *Ergebn. d. allg. Path. u. path. Anat.* **13**:298, 1909.
241. —Zur Pathologie und Klinik der primären Atherosklerosis pulmonalis, *Wien. Arch. f. inn. Med.* **11**:357, 1925.
242. Prevot, H.: Ueber Verfettung der Lungenvenen, *Centralbl. f. allg. Path. u. path. Anat.* **50**:305, 1931.
243. Pund, E. R., and Phinzy, T. B.: Primary Sclerosis of the Pulmonary Artery, *Ann. Int. Med.* **5**:1391, 1932.
244. Quain, J.: *Elements of Anatomy*, ed. 11, New York, Longmans' Green & Co., 1900, vol. 2, pt. 2, p. 378; vol. 3, pt. 4, p. 185.
245. Querat, Gaudy, and Deguignaud: Cardiopathie congénitale (rétrécissement mitral et dilatation de l'artère pulmonaire), vraisemblablement d'origine hérédo-syphilitique, *Bull. et mém. Soc. méd. d. hôp. de Paris* **45**:608, 1921.
246. Ramond: Hypertension artérielle pulmonaire, *Presse méd.* **37**:1079, 1927.
247. Reeke, T.: Ueber Syphilis der Pulmonalarterie, *Centralbl. f. allg. Path. u. path. Anat.* **49**:257, 1930.
248. Ribadeau-Dumas, L., and Chabrun, L.: Adénitis pulmonaires du nourisson, *Bull. et mém. Soc. méd. d. hôp. de Paris* **51**:402, 1927.
249. Ribbert, H.: Ueber den Bau der in die Pulmonalarterie embolisierten Thromben, *Deutsche med. Wchnschr.* **40**:1409, 1914.
250. Ribierre, P., and Giroux, R.: Sclérose de l'artère pulmonaire secondaire à des processus broncho-pulmonaires, *Bull. et mém. Soc. méd. d. hôp. de Paris*, **45**:1465, 1921.
251. Rist, E., and Rolland, J.: Contribution a l'étude clinique, anatomique et pathogénique des infarctus et hémorrhagies pulmonaire, *Ann. de méd.* **20**:307, 1926.
252. Rössle, R.: Ueber Hypertrophie und Organkorrelation, *München. med. Wchnschr.* **55**:377, 1908.
253. Roger, H., and Binet, L.: Le processus histologique de la lipodiérèse pulmonaire, *Compt. rend. Soc. de biol.* **88**:1140, 1923.
254. Rogers, L.: Extensive Atheroma and Dilatation of the Pulmonary Arteries Without Marked Valvular Lesions as a Not Very Uncommon Cause of Fatal Cardiac Disease in Bengal, *Quart. J. Med.* **2**:1, 1908.
255. Romberg, E.: Ueber Sklerose der Lungenarterie, *Deutsches Arch. f. klin. Med.* **48**:197, 1891.
256. Rosenthal, S. R.: Sclerosis of the Pulmonary Artery and Arterioles, *Arch. Path.* **10**:717 (Nov.) 1930.
257. —Isolated Giant Growth of a Branch of the Pulmonary Artery Associated with Congenital Bronchiectasis, *ibid.* **12**:387 (Sept.) 1931.
258. Rossiter, C. B.: High Blood Pressure, *Lancet* **1**:132, 1933.

259. Roth, O.: Ueber primäre Endarteritis pulmonalis; zugleich ein Beitrag zur Prognose des offenen Ductus Botalli, *Ztschr. f. Kreislaufforsch.* **19**:537, 1927.
260. Rouslacroix and Perimonde: Insuffisance du coeur droit chez un bronchitique emphysémateux; thrombose de la branche droite de l'artère pulmonaire; dilatation permanente, et insuffisance de ce vaisseau, *Paris méd.* **2**:499, 1925.
261. Rühl, A.: Wie weit ist der genuine arterielle Hochdruck anatomisch bedingt? *Deutsche med. Wchnschr.* **156**:129, 1927.
262. Ruppert, H.: Vier Krankengeschichten mit Sectionsbefund aus der Pathologie des Gefäß-systems, *Beitr. z. path. Anat. u. z. allg. Path.* 1905, supp. 7, p. 174.
263. Salzer, G.: Ueber zwei Fälle von eitriger Entzündung der Lungenschlagader, *Centralbl. f. allg. Path. u. path. Anat.* **41**:100, 1928.
264. Sanders, W. E.: Primary Pulmonary Arteriosclerosis with Hypertrophy of the Right Ventricle, *Arch. Int. Med.* **3**:257 (April) 1909.
265. Saphir, O.: Bands and Ridges in the Pulmonary Artery, *Arch. Path.* **14**:10 (July) 1932.
266. Scarff, J. E.: Pulmonary Blood Pressures, *Arch. Surg.* **12**:591 (Feb.) 1926.
267. Schlaepfer, K.: Morphological Changes Associated with Partial Occlusion of the Pulmonary Veins, *Surg., Gynec. & Obst.* **42**:679, 1926.
268. —The Effect of Ligation of the Pulmonary Artery of One Lung With and Without Resection of the Phrenic Nerve, *Arch. Surg.* **13**:623 (Nov.) 1926.
269. —Chronic and Acute Arteritis of the Pulmonary Artery and of the Patent Ductus Arteriosus, *Arch. Int. Med.* **37**:473 (April) 1926.
270. Schlesinger, H.: Zur Diagnostik und Klinik der Pulmonalarterienerkrankungen, *Wien. klin. Wchnschr.* **40**:1194, 1927.
271. Schmidt, M. B.: Die Verbreitungswege der Karzinome, Jena, Gustav Fischer, 1903; quoted by Krutsch.¹⁵¹
272. Schoen, R.: Ueber die Stauung im Lungenkreislauf, *Deutsche klin. Wchnschr.* **9**:1849, 1930.
273. Schramm, H. G.: Beiträge zur Aetiologie der Thrombose der Arteria pulmonalis **19**:718, 1927.
274. Schreyer, W.: Polycythaemia und Pulmonalarterienerweiterung, *Deutsches Arch. f. klin. Med.* **148**:149, 1925.
275. Schütte, H.: Rechtsseitige Herzhypertrophie hervorgerufen durch eine entzündliche Veränderung der kleinen Lungenarterien, *Centralbl. f. allg. Path. u. path. Anat.* **25**:483, 1914.
276. Schwartz, G.: Ueber einen Fall von abundanter Lungenblutung bei Mitralkstenose und hochgradige Sklerose der Arteria pulmonalis, *München. med. Wchnschr.* **54**:615, 1907.
277. Schwartz, S. P.: The Radiographic Signs of Pulmonic Insufficiency, *Am. Heart J.* **2**:407, 1927.
278. Scott, R. B.: Aneurysm of the Pulmonary Artery, *Lancet* **1**:567, 1934.
279. Shaw, R. C.: Nerve Irritation and Aortic Lesions, *Quart. J. Med.* **19**:203, 1926.
280. Slater, S. R.: Involvement of the Coronary Arteries in Acute Rheumatic Fever, *Am. J. M. Sc.* **181**:203, 1931.
281. Sokoloff, M. J., and Stewart, H. L.: Hyperplastic Sclerosis of the Pulmonary Arteries and Arterioles, *Arch. Int. Med.* **51**:403 (March) 1933.

282. Stadelmann, E.: Ueber Thrombosen der Pulmonalarterien, *Deutsche med. Wchnschr.* **35**:1089, 1909.
283. Stadler, E.: Syphilis des Herzens und der Gefäße, in Grote, L. R.; Fromme, A., and Warnekros, K.: *Medizinische Praxis: Sammlung für ärztliche Fortbildung*, Dresden, Theodor Steinkopff, 1932, vol. 16.
284. Steinberg, U.: Ueber sekundäre Pulmonalarteriensklerose, *Beitr. z. path. Anat. u. z. allg. Path.* **82**:307, 1929.
285. —Zur Frage der primären Pulmonalsklerose, *ibid.* **82**:443, 1929.
286. Sternberg, H.: Ueber zwei Fälle von Durchbruch der Aorta in die Arteria pulmonalis, *Wien. klin. Wchnschr.* **32**:1024, 1919.
287. Sternberg, C.: Tödliche Lungenblutung infolge Periarteriitis nodosa, *Wien. klin. Wchnschr.* **38**:729, 1925.
288. Stevens, G. A.: A Case of Atheroma of the Pulmonary Artery, *Lancet* **1**:1295, 1931.
289. Stewart, G. N.: The Pulmonary Circulation Time, the Quantity of Blood in the Lungs, and the Output of the Heart, *Am. J. Physiol.* **58**:20, 1921-1922.
290. Stoerk, A., and Epstein, E.: Ueber arterielle Gefäßveränderungen bei Grippe, *Frankfurt. Ztschr. f. Path.* **23**:163, 1920.
291. Stopford, J. S. B.: The Innervation of the Blood Vessels of the Limbs, *Lancet* **2**:779, 1931.
292. Sutherland, G. A.: A Case of Congenital Aneurysm of the Pulmonary Artery, *Brit. J. Child. Dis.* **20**:27, 1923.
293. Swift, H. S., and Hitchcock, C. H.: Cardiac Pain in Rheumatic Fever, *Tr. A. Am. Physicians* **62**:228, 1927.
294. Thayer, W. S.: Studies in Bacterial Endocarditis, *Johns Hopkins Hosp. Rep.* **22**:1, 1926.
295. Thomas, M.: Contribution à l'étude des affections acquises de l'artère pulmonaire, Thèse de Paris, no. 474, Paris, Félix Alcan, 1927.
296. Torhorst, H.: Die histologischen Veränderungen bei Sklerose der Pulmonalarterie, *Beitr. z. path. Anat. u. z. allg. Path.* **36**:210, 1904.
297. Tournade, A.: Technique de la prise de pression dans l'artère pulmonaire, *Compt. rend. Soc. de biol.* **109**:1128, 1932.
298. Tremolières, F.; Tardieu, A., and Nativelle, R.: Artérite pulmonaire subaigüe chez un syphilitique atteint de maladie mitrale, *Bull. et mém. Soc. méd. d. hôp. de Paris* **52**:860, 1928.
299. Trunicek, C.: L'hypertension de la petite circulation, *Rev. de méd., Paris* **44**:1161, 1927.
300. Tschistowitsch, T.: Thrombo-endartérite pulmonaire, *Compt. rend. Soc. de biol.* **89**:627, 1923.
301. Turnbull, H. M.: Alterations in Arterial Structure, and Their Relation to Syphilis, *Quart. J. Med.* **8**:201, 1914-1915.
302. Ulrich, H. L.: The Clinical Diagnosis of Pulmonary Arteriosclerosis, *Ann. Int. Med.* **6**:632, 1932.
303. Underhill, S. W.: An Investigation into the Circulation Through the Lungs, *Brit. M. J.* **2**:779, 1921.
304. Vaquez, H.: Sclérose de l'artère pulmonaire, *Paris méd.* **2**:15, 1926.
305. —and Bordet, E.: Radiologie du coeur et des vaisseaux de la base, Paris, J. B. Baillière et fils, 1928.
306. —and Giroux, L.: Artériosclérose généralisée de l'artère pulmonaire avec athérome, *Bull. et mém. Soc. méd. d. hôp. de Paris* **26**:183, 1908.
307. Veale, P. J., and Coombs, C. F.: Cardiac Failure in a Child Aged Six Years Associated with Atheroma of the Pulmonary Artery and Extreme Dilatation of the Right Ventricle, *Brit. J. Child. Dis.* **12**:72, 1915.

308. Wätjen, J.: Isolierte Sklerose der Pulmonalarterie im jüngsten Kindesalter, *Deutsche med. Wchnschr.* **50**:713, 1924.
309. Wahl, H. R., and Gard, R. L.: Aneurysm of the Pulmonary Artery, *Surg., Gynec. & Obst.* **52**:72, 1931.
310. Waring, J. J., and Yegge, W. B.: Polycythaemia in Association with Pulmonary Disorders, *Ann. Int. Med.* **7**:190, 1933.
311. Warthin, A. S.: Syphilis of the Pulmonary Artery; Syphilitic Aneurysm of the Left Upper Division; Demonstration of the Spirochaeta Pallida in the Wall of the Artery and the Aneurysmal Sac, *Am. J. Syph.* **1**:693, 1917.
312. Wartman, W. B.: The Incidence and Severity of Arteriosclerosis in the Organs from 500 Autopsies, *Am. J. M. Sc.* **186**:27, 1933.
313. Wassiljeff, A. A., and Argun, A. M.: Zur Frage der gummösen Erkrankung der Lungenschlagader, *Centralbl. f. allg. Path. u. path. Anat.* **47**:327, 1929.
314. Wearn, J. T.; Barr, J. S., and German, W. J.: The Behavior of the Arterioles and Capillaries of the Lungs, *Proc. Soc. Exper. Biol. & Med.* **24**:114, 1926.
315. Weber, F. P.: Sur la signification pronostique de la polycythémie secondaire dans les affections cardio-pulmonaires, *Arch. d. mal. du coeur* **6**:266, 1913.
316. —The Secondary Forms of Polycythaemia Rubra, *Brit. M. J.* **2**:658, 1920.
317. Weil, S. S.: Ueber eigenartige Formen der Gefäß-syphilis, *Virchows Arch. f. path. Anat.* **265**:414, 1927.
318. Weiss, S.: Circulatory Adjustments in Heart Disease; a Concept of Circulatory Failure, *Ann. Int. Med.* **5**:100, 1931.
319. —and Blumgart, H. L.: The Velocity of the Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Pulmonary Emphysema, *J. Clin. Investigation* **4**:555, 1927.
320. —and Ellis, L. B.: The Quantitative Aspects and Dynamics of the Circulation in Arterial Hypertension, *Am. Heart J.* **5**:448, 1929-1930.
321. Wells, H. G.: The Chemistry of Arteriosclerosis, in Cowdry, E. V.: *Arteriosclerosis*, New York, The Macmillan Company, 1933, p. 323.
322. White, P. D.: The Relationship of the Heart and Lungs in Disease, *Arch. Surg.* **18**:339 (Jan.) 1929.
323. —and Brenner, O.: Pathological and Clinical Aspects of the Pulmonary Circulation, *New England J. Med.* **209**:1261, 1933.
324. Wiesel, J., and Löwy, R.: Die Erkrankungen der peripheren Arterien im Verlaufe der akuten und chronischen Kreislaufschwäche, *Wien. Arch. f. inn. Med.* **1**:197, 1920.
325. —Zur Pathologie der Lungengefäße, *Wien. klin. Wchnschr.* **34**:289, 1921.
326. Wiggers, C. J.: The Regulation of the Pulmonary Circulation, *Physiol. Rev.* **1**:239, 1921.
327. Winter, R.: Ueber die Entstehung von Thromben im rechtem Herzen und in den Aesten der Lungenschlagader auf dem Boden von Krebszellembolien, *Virchows Arch. f. path. Anat.* **282**:99, 1931; abstr., *Ztschr. f. Kreislaufforsch.* **25**:217, 1933.
328. Wodinski, quoted by Durand.⁸⁸
329. Wolfram, A.: *Gaz. lek.*, 1883, no. 24, p. 25; quoted by Romberg.²⁵⁵
330. Wolheim, E.: Zur funktionellen Bedeutung der Cyanose, *Ztschr. f. klin. Med.* **108**:248, 1928.

331. Yater, W. M., and Constam, G. R.: Pulmonary Arteriosclerosis, *M. Clin. North America* **12**:1689, 1929.
332. Zeek, P.: Conditions in Childhood Predisposing to the Early Development of Arteriosclerosis, *Am. J. M. Sc.* **184**:350, 1932.
333. —Atheroma and Its Sequelae in Rheumatic Heart Disease, *ibid.* **184**:356, 1932.
334. Zeman, F. D.: Syphilitic Atherosclerosis Presenting Clinically the Symptoms of Ayerza's Disease, *Proc. New York Path. Soc.* **23**:58, 1923.
335. Zinsser, H.: Notes on Arteriosclerosis of the Pulmonary Arteries, *Proc. New York Path. Soc.* **8**:74, 1908.

EFFECT OF THEOPHYLLINE ETHYLENEDIAMINE ON EXPERIMENTALLY INDUCED CARDIAC INFARCTION IN THE DOG

W. M. FOWLER, M.D.

H. M. HUREVITZ, M.D.

AND

FRED M. SMITH, M.D.

IOWA CITY

Until recent years the various xanthine derivatives were employed in the treatment of cardiac disease chiefly because of their diuretic action. The discovery that these preparations cause dilatation of the coronary arteries and the introduction of theophylline ethylenediamine in 1908¹ led to a further study of this particular pharmacologic action.

Eppinger and Hess² observed a stretching of strips of coronary arteries when they were placed in a solution of caffeine, and Gow,³ employing a similar method, noted a dilatation of arterial rings taken from the renal and splenic arteries. Hedbom⁴ was among the first to study the problem by the perfusion method and reported an increase in the coronary flow with caffeine in a concentration of 1:20,000. Loeb⁵ observed a marked increase in the rate of perfusion with theobromine but very little effect with caffeine. Heathcote,⁶ working with caffeine, theobromine and theophylline in concentrations from 1:2,000 to 1:40,000, obtained a marked increase in the rate of perfusion with the higher concentrations, but in dilutions of 1:20,000 and 1:40,000 caffeine

From the Department of Internal Medicine, State University of Iowa.

Presented before the meeting of the American Society for Clinical Investigation, Atlantic City, N. J., April 30, 1934.

1. Dessauer, P.: Euphyllin, neues Diuretikum, *Therap. Monatsh.* **22**:401, 1908.

2. Eppinger, H., and Hess, L.: Versuche über die Einwirkung von Arzneimitteln auf überlebende Coronargefäße, *Ztschr. f. exper. Path. u. Therap.* **5**:622, 1909.

3. Gow, D.: Some Reactions of Surviving Arteries, *J. Physiol.* **42**:125, 1911.

4. Hedbom: *Skandinav. Arch. f. Physiol.* **9**:1, 1899; cited in *Therapeutic Claims for Theobromine and Theophyllin Preparations*, report of the Committee on Pharmacy and Chemistry, *J. A. M. A.* **94**:1306 (April 26) 1930.

5. Loeb, O.: Ueber die Beeinflussung des Koronarkreislaufs durch einige Gifte, *Arch. f. exper. Path. u. Pharmakol.* **51**:64, 1904.

6. Heathcote, R. St. A.: The Action of Caffeine, Theobromine and Theophylline on the Mammalian and Batrachian Heart, *J. Pharmacol. & Exper. Therap.* **16**:327, 1920.

produced no change, theobromine very little and theophylline from 20 to 30 per cent increase. Guggenheimer and Sassa,⁷ using the isolated heart of a cat, found that caffeine in a dilution of 1:25,000 increased the rate of perfusion 41 per cent. Theophylline and theophylline ethylenediamine in similar concentrations produced an increase of 40 and 80 per cent, respectively. More recently, Smith, Miller and Graber⁸ studied the effects of certain of these drugs by perfusion experiments on the isolated heart of a rabbit. Caffeine sodiobenzoate in a concentration of 1:25,000 did not produce a significant change in the rate of perfusion. Theobromine sodiosalicylate in the same concentration did not produce a change, but when a concentration of 1:50,000 was employed a slight increase in the rate of perfusion was noted. Theophylline in concentrations of 1:25,000 and 1:50,000 augmented the coronary flow from 20 to 45 per cent, while theophylline ethylenediamine in similar concentrations increased the rate of flow from 40 to 90 per cent.

These aforementioned investigators subsequently studied the action of theophylline and theophylline ethylenediamine on the intact dog by means of the Morowitz-Zahn cannula and obtained comparable results.⁹ Various other workers have employed the intact animal in the investigation of this problem. Meyer,¹⁰ recording the flow from a coronary vein, reported that the intravenous administration of caffeine is followed by an increase in the rate of coronary flow, but he attributed this result to an elevation in the systemic blood pressure. Sakai and Saneyoshi,¹¹ from experiments on the intact heart in which they employed the Morovitz-Zahn cannula, obtained an increased flow with average and large doses of theobromine sodiosalicylate.

Fisher, Guggenheimer and Müller,¹² working with the heart-lung preparation, studied the action of theophylline ethylenediamine,

7. Guggenheimer, H., and Sassa, K.: Ueber die Beeinflussung des Coronarkreislaufs durch Purinderivate, *Klin. Wchnschr.* **2**:1451, 1923.

8. Smith, F. M.; Miller, G. H., and Graber, V. C.: The Effects of Caffeine Sodiobenzoate, Theobromin Sodiosalicylate, Theophyllin and Euphyllin on the Coronary Flow and Cardiac Action of the Rabbit, *J. Clin. Investigation* **2**:157, 1925.

9. Smith, F. M., and Miller, G. H.: The Study of the Action of Theophyllin and Theobromine on the Coronary Circulation of the Intact Heart, *Am. J. Physiol.* **85**:407, 1928.

10. Meyer, F.: Ueber die Wirkung verschiedener Arzneimittel auf die Coronargefäße des lebenden Tieres, *Arch. f. Physiol.*, 1912, p. 223.

11. Sakai, S., and Saneyoshi, S.: Ueber die Wirkung einiger Herzmittel auf die Koronargefäße, *Arch. f. exper. Path. u. Pharmakol.* **78**:331, 1915.

12. Fisher, I.; Guggenheimer, H., and Müller, E. A.: Ueber die Beeinflussung von Koronardurchblutung und Herztonus durch Theophyllinpräparate und Strophanthin nach Untersuchungen am Starlingschen Herz-Lungenpräparat, *Deutsche med. Wchnschr.* **54**:1584, 1928.

theophylline and strophanthin. There was a distinct increase in the rate of coronary flow after the administration of theophylline ethylenediamine and theophylline, whereas a decrease was noted after the administration of strophanthin. More recently, Gilbert and Fenn,¹³ using the intact animal, found theobromine and its salts to be the most effective and caffeine sodiobenzoate the least effective in increasing the coronary flow. Intermediate effects were obtained with theophylline ethylenediamine and theophylline sodio-acetate.

Because of the discrepancy in the results obtained by various investigators and as a preliminary step to the further study of this question, the perfusion experiments on the isolated heart of the rabbit were repeated. It is to be noted in the table that of the various preparations

*The Percentage Increase in the Coronary Flow with the Various Preparations **

	Dilution			
	1:15,000	1:25,000†	1:30,000	1:60,000
Glycoeyamine.....	18.21	35.32	15.38
Caffeine sodiobenzoate.....	20.53
Sodium nitrite.....	62.91
Theobromine sodio-acetate.....	42.87	32.14
Theophylline sodio-acetate.....	29.18
Theophylline mono-ethanolamine.....	27.35	51.13	38.46	11.21
Theophylline ethylenediamine.....	96.65	38.8
Sodium nitrite 1:50,000 and theophylline ethylenediamine 1:25,000.....				81.98
Glycoeyamine 1:50,000 and theophylline ethylenediamine 1:25,000.....				56.07
Glycoeyamine 1:50,000 and theobromine sodio-acetate 1:50,000.....				32.22

* The figures represent the average increase obtained in from two to twenty trials.

† An intravenous preparation of theophylline ethylenediamine was used in the 1:20,000 dilution, whereas the tablet form was used in the 1:30,000 dilution.

employed, theophylline ethylenediamine was by far the most effective. The augmentation of the coronary flow was usually associated with an increase in the rate and amplitude of cardiac contraction, but there was no definite correlation between the increased amplitude and the increase in coronary flow. Moreover, it has been shown⁸ that the increase in the cardiac rate does not appreciably affect the rate of perfusion. Of the various drugs employed, theophylline ethylenediamine had the most beneficial effect on the myocardium, as evidenced by the disappearance of irregularities in certain instances and an increase in the amplitude of cardiac contraction. Combinations of various drugs were tried, but these were no more effective than theophylline ethylenediamine alone. In view of the aforementioned results, theophylline ethylenediamine was selected for a more decisive test of its dilating action on the coronary vessels.

13. Gilbert, N. C., and Fenn, G. K.: The Effect of the Purine Base Diuretics on the Coronary Flow, *Arch. Int. Med.* **44**:118 (July) 1929.

EXPERIMENTAL OBSERVATIONS

Immediate Effects.—Six dogs were utilized in a study of the immediate effects of theophylline ethylenediamine on the coronary circulation. Ethyl carbamate (urethane) supplemented by a small amount of ether served as the anesthetic, and artificial respiration was maintained by intermittent positive pressure through a tracheal catheter. A continuous record of the blood pressure was obtained from the carotid artery. The thoracic wall was incised, and the pericardium was opened. The edges of the pericardial slit were sutured to those of the thoracic incision, forming a support for the heart. The anterior descending branch of the left coronary artery, together with the accompanying vein, was ligated just above the origin of the last main branch. Almost immediately an area of cyanosis appeared distal to the ligation. This gradually increased in size and reached its maximum extent in about five minutes. Theophylline ethylene-

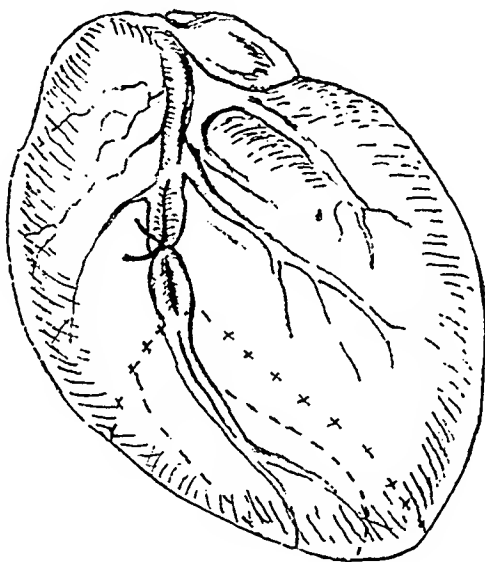


Fig. 1.—The crisscross line indicates the outline of the cyanotic area immediately after ligation of the coronary vessels. The line of dashes represents the outline of the cyanotic area after the intravenous administration of theophylline ethylenediamine.

diamine was then administered intravenously, and the effects on the cyanosis and blood pressure were noted.

In the first three animals 2 cc. (0.48 Gm.) of the drug was injected into the femoral vein. A change in the area of cyanosis was apparent within two minutes after the injection, and the maximum effect was reached within five minutes. The edges of the cyanotic area, which prior to the administration of the drug had been sharply defined, became blurred, indistinct and irregular and gradually receded toward the ligated vessel. The extent to which the area of cyanosis disappeared varied from animal to animal, but from 50 to 90 per cent of the cyanosed area was restored to normal color in each instance and became indistinguishable from the uninvolved surrounding area. In the two animals showing the most striking regression the wall of the left ventricle was almost completely cleared of cyanosis, and the only remaining discoloration was confined to a small area on the wall of the right ventricle adjacent to the ligated vessel. The disappearance of the cyanosis was associated with a rather prompt drop in the blood

pressure ranging from 40 to 55 mm. of mercury. There was little tendency for the blood pressure to return to the original level.

In the fourth animal there was a striking reduction in the extent and degree of cyanosis, accompanied by a drop in blood pressure from 102 to 55 mm. Injection of hypertonic solution of dextrose (40 cc. of a 50 per cent solution) was followed by a return of the blood pressure to approximately the original level without a reappearance of the cyanosis.

In the remaining two animals theophylline ethylenediamine was diluted in a 50 per cent solution of dextrose and introduced slowly and intermittently over a period of thirty minutes. After each small injection the blood pressure dropped from 6 to 12 mm. but returned promptly to the original level. By this method of administration there was a striking reduction in the area of cyanosis, while the blood pressure was maintained at approximately a constant level. After reduction of the cyanosis by the administration of theophylline ethylenediamine, epi-

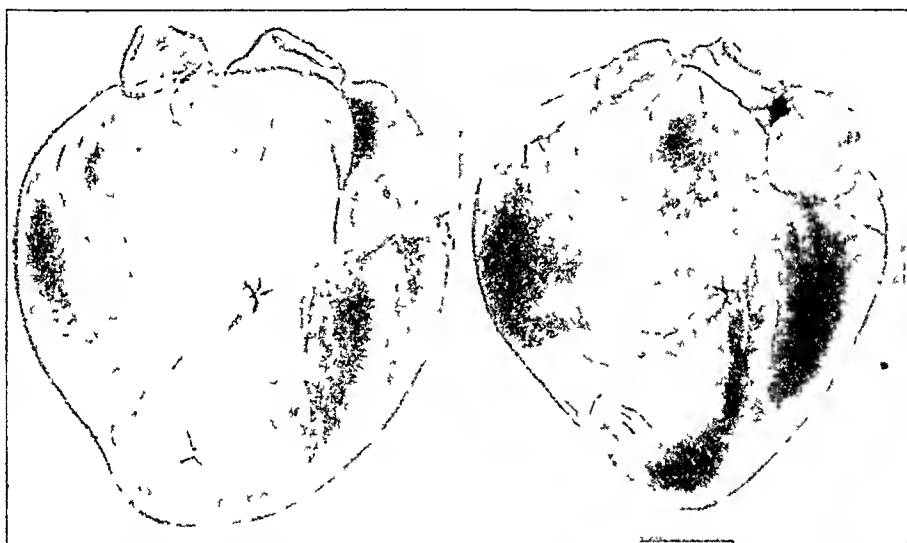


Fig. 2—Drawings showing the size of the myocardial infarction in the control animals at the end of three weeks.

nephrene (0.2 cc. of a 1:1,000 solution) was given intravenously. There was a prompt elevation of the blood pressure, with a return of the area of cyanosis to its original extent. The area of cyanosis was again dispersed by the injection of theophylline ethylenediamine. At the termination of these experiments, about one and one-half hour after the ligation of the vessel, the blood pressure was within 12 mm. of the original level, and about 75 per cent of the area of cyanosis had been restored to normal color.

Late Effects.—In nineteen dogs the anterior descending limb of the left coronary artery was ligated just below the origin of the last main branch. Slight variations in the arterial distribution were encountered in a few instances, but the ligature was placed as nearly as possible at a constant level. The dogs were examined at autopsy three weeks after the operation, and the extent of the myocardial infarction was carefully studied. The first ten of these animals served as controls, whereas the remaining nine were given theophylline ethylenediamine, 3 grains (0.195 Gm.) daily, after the operation.

In the ten control animals the coronary artery was found to be completely occluded in all instances, with a resultant area of myocardial fibrosis distal to the ligation. The infarct began immediately below the ligature and extended to the apex and in most instances beyond this point to the posterior wall of the left ventricle. The infarct gradually increased in width, reaching its maximum a short distance above the apical region. The wall of the left ventricle bore the brunt of the injury in all instances, but the adjacent wall of the right ventricle was always involved to some extent. The interventricular septum was invaded by fibrous tissue to a varying degree in each animal. The outline of the infarcted area was irregular and presented a frayed-out or fringelike appearance, due to the extension of fine streaks of fibrous tissue into the surrounding musculature. The endocardium immediately beneath the area of greatest myocardial damage presented a whitish discoloration. In seven of the ten animals the wall of the left ventricle near the apex was greatly diminished in thickness, and the muscu-



Fig. 3.—Drawings showing the size of infarction at the end of three weeks in the dogs that received theophylline ethylenediamine.

lature consisted entirely of fibrous tissue. In the other three dogs the replacement of fibrous tissue appeared just as extensive, although there was no evident reduction in the thickness of the wall.

Nine animals were given theophylline ethylenediamine, 3 grains daily, throughout the postoperative course. In one of these the coronary artery was not completely occluded, and the heart was discarded. In two animals the drug was injected intramuscularly, and sterile abscesses developed at the site of injection. Although the absorption was probably incomplete in these animals, the extent of the infarction was considerably less than that in the control series. They presented, however, a rather extensive fibrosis. In the remaining six animals the drug was given by mouth, first by a stomach tube for a few days immediately following the operation and later concealed in a bit of food. The area of fibrosis was markedly diminished and was a narrow strip parallel to the course of the ligated vessel, with no tendency to increase in width as it approached the apex. The length of the infarcted area was distinctly reduced, as it never extended

beyond the apex and in most cases disappeared proximal to this point. The outline of the infarct was sharply demarcated, with few strands of fibrous tissue extending into the adjacent musculature. In no instance was there a demonstrable reduction in the thickness of the wall of the left ventricle, and on cut section the myocardium of this chamber presented a surprisingly normal appearance. The extent of involvement in the interventricular septum was greatly reduced, and there were instances in which there was no apparent endocardial involvement. The extent of fibrosis on the wall of the right ventricle was reduced but slightly, so that this region presented the most extensive damage in this group of animals. It is of interest that this area corresponded exactly with the area of persistent cyanosis in the preceding experiment.

COMMENT

The effects of theophylline ethylenediamine on the coronary circulation has been demonstrated by the increased rate of perfusion in the isolated heart of the rabbit, by the regression of the area of cyanosis appearing immediately after the ligation of a coronary vessel in the dog and, finally, by the marked reduction in the extent of fibrosis in survival experiments. There are obvious objections to the perfusion method of testing the action of drugs on the coronary circulation, but the observations on the intact heart in the foregoing experiments in our opinion demonstrate conclusively the dilating action of theophylline ethylenediamine.

The extent of the cardiac infarction in cases of coronary occlusion is determined by the size of the vessel occluded and the effectiveness of the collateral circulation. It is apparent that treatment should be directed toward the restoration of the circulation to the damaged area. In the experiments reported here the changes observed both as to early and as to late effect were no doubt dependent on the action of the drug on the collateral circulation. While in the experimental animal we were dealing with normal vessels, the character of the results obtained recommended the use of theophylline ethylenediamine in the treatment of acute coronary occlusion. Our clinical results so far are in accord with what might be expected from the experimental study.

In order to conserve the cardiac musculature of the infarcted area to the maximum extent through the development of the collateral circulation, the medication should be employed early in the course of acute coronary occlusion and should be continued until there is sufficient time for the infarct to heal. Intravenous administration of the drug, for at least the initial dose, insures a more prompt response and in certain instances is justifiable. In our experience the slow administration of the drug ordinarily prevents any untoward effects from a reduction in the blood pressure. Experimental observations indicate that the combination with hypertonic solution of dextrose may provide an additional safeguard against this possibility.

CONCLUSION AND SUMMARY

The experiments reported here have demonstrated that theophylline ethylenediamine promotes the development of the collateral circulation in experimentally induced cardiac infarction in the dog. The results justify the use of this preparation in the treatment of disease of the coronary arteries and acute coronary occlusion.

THEOPHYLLINE IN THE TREATMENT OF DISEASE OF THE CORONARY ARTERIES

FRED M. SMITH, M.D.

IOWA CITY

HERBERT W. RATHE, M.D.

WAVERLY, IOWA

AND

W. D. PAUL, M.D.

IOWA CITY

The reduction in the coronary circulation through the gradual encroachment on the lumen due to sclerotic changes and, finally, the occlusion of vessels of varying size is primarily responsible for the cardiac disability in disease of the coronary arteries. It is thus important that treatment be directed toward the restoration and maintenance of an effective coronary circulation in this form of cardiac disease. Various remedies, particularly the xanthine derivatives, have been recommended for this purpose. In a previous communication¹ experimental data concerning the effectiveness of these preparations were reviewed, and additional observations relative to the dilating action of theophylline ethylenediamine were reported. The latter experiments in our opinion conclusively demonstrated the dilating action of this preparation on the coronary arteries of the dog.

The xanthine derivatives are well known for their diuretic action, and it is generally conceded that theophylline is the most effective of the group. Marvin² has shown that the diuretic action of xanthine derivatives is most marked in cases of congestive failure of arteriosclerotic cardiac disease. It would seem, as suggested by one of us in a previous report,³ that the effectiveness of the preparations under the aforementioned conditions is probably enhanced by the improvement in the function of the myocardium through the dilating action on the coronary vessels.

From the Department of Internal Medicine, State University of Iowa College of Medicine.

Presented at the Tenth Scientific Session of the American Heart Association, Cleveland, June 12, 1934.

1. Fowler, W. M.; Hurevitz, H. M., and Smith, Fred M.: The Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction, *Arch. Int. Med.*, this issue, p. 1242.

2. Marvin, H. M.: The Value of the Xanthine Diuretics in Congestive Heart Failure, *J. A. M. A.* **87**:2043 (Dec. 18) 1926.

3. Smith, Fred M.: The Diet and Theophyllin in the Treatment of Cardiac Failure, *J. A. M. A.* **91**:1274 (Oct. 27) 1928.

Askanazy⁴ was apparently the first to recommend the use of the xanthine derivatives in disease of the coronary arteries, having observed favorable results from the employment of theobromine sodiosalicylate in cases of angina pectoris and occasionally striking improvement in patients with cardiac asthma, with or without anginal pain. These results were later confirmed by Breuer,⁵ who particularly emphasized the importance of this remedy in the treatment of angina pectoris and cardiac asthma. Dessauer⁶ in 1908 introduced theophylline ethylenediamine and reported striking diuretic action in patients with congestive cardiac failure. The addition of ethylenediamine to theophylline produced a more soluble and less irritating combination. Guggenheimer⁷ observed favorable results from the use of theophylline ethylenediamine in patients with arteriosclerotic cardiac disease without edema, which he was inclined to attribute to the probable dilating action on the coronary vessels. This led to the experimental investigation of this feature by Guggenheimer and Sassa.⁸

The widespread interest in diseases of the coronary arteries during recent years again directed attention to the xanthine derivatives and stimulated further experimental and clinical study of the action of these preparations on the coronary vessels. Certain of these experimental studies were reviewed in the previous communication.¹ In the meantime, clinical reports by Smith, Miller and Graber,⁹ Dock,¹⁰ Musser,¹¹ Vogl,¹² Gilbert and Kerr,¹³ Guggenheimer¹⁴ and others appeared in the

4. Askanazy, S.: *Klinisches über Diuretin*, *Deutsches Arch. f. klin. Med.* **56**:209, 1895.

5. Breuer, R.: *Zur Therapie und Pathogenese der Stenokardie und verwandte Zustände*, *München. med. Wchnschr.* **49**:1604, 1902.

6. Dessauer, P.: *Euphyllin ein neues Diuretikum*, *Therap. Monatsh.* **22**:401, 1908.

7. Guggenheimer, H.: *Zur Herzbehandlung bei Erkrankungen der Koronargefäße*, *Deutsche med. Wchnschr.* **49**:1007, 1923.

8. Guggenheimer, H., and Sassa, K.: *Ueber die Beeinflussung des Coronarkreislaufs durch Purinderivate*, *Klin. Wchnschr.* **2**:1451, 1923.

9. Smith, Fred M.; Miller, G. H., and Graber, V. C.: *The Study of the Action of Euphyllin in Cardiac Failure Associated with Arteriosclerosis*, *Tr. Sect. Pharmacol. & Therap., A. M. A.*, 1926, p. 171.

10. Dock, William: *The Use of Theobromine for Pain of Arteriosclerotic Origin*, *California & West. Med.* **25**: 636, 1926.

11. Musser, J. H.: *Theophylline-Ethylenediamine in Heart Disease Associated with Pain*, *J. A. M. A.* **91**:1242 (Oct. 27) 1928.

12. Vogl, A.: *Erfahrungen über Euphyllin bei Cheyne-Stokes und anderen Formen zentraler Atemstörungen*, *Med. Klin.* **28**:9, 1932.

13. Gilbert, N. C., and Kerr, John Austin: *Clinical Results in Treatment of Angina Pectoris with the Purine Base Diuretic*, *J. A. M. A.* **92**:201 (Jan. 19) 1929.

14. Guggenheimer, H.: *Ueber die Wirkungsweise des Euphyllins bei kardio-vasculärem Cheyne-Stokes und Asthma cardiale*, *Ztschr. f. Kreislaufforsch.* **25**: 98, 1933.

literature. These observations were concerned with the effectiveness of theophylline, chiefly in the form of theophylline ethylenediamine or the preparations of theobromine, for patients with angina pectoris or paroxysmal dyspnea. In certain instances in each of these series, favorable or even striking results were obtained. The report by Gilbert and Kerr, based on the study of 86 cases of angina pectoris, is of particular significance in that the patients were ambulatory and were permitted to continue with their regular activities and no other medication was employed. Observations were made on the effect of preparations of theobromine, theophylline and theophylline ethylenediamine. These observers were careful in the interpretation of their results, realizing the marked variation in the clinical course of the disorder and the variety of means by which it may be influenced. In this series of 86 cases there were only 14 patients who obtained no relief from any preparation used. The remaining 72 showed varying degrees of improvement.

In this communication we wish to report our experience covering a period of eight years with the use of theophylline and theophylline ethylenediamine in the treatment of disease of the coronary arteries, manifested by congestive failure, paroxysmal dyspnea, angina on effort or occlusion of the coronary arteries. The preparations of theophylline were employed exclusively, because in the experimental study made by Smith, Miller and Graber,⁹ on both the isolated and the intact heart, these substances had a more pronounced action on the coronary circulation than the other xanthine derivatives.

These preparations were prescribed as a routine in the treatment of congestive failure, not only because of their diuretic action but because of their favorable influence on the coronary circulation. The onset of the cardiac disability in cases of disease of the coronary arteries is commonly marked by shortness of breath, followed in time by congestive failure. Of a series of 420 cases reported¹⁵ this type of onset occurred in 189.

From 1½ to 3 grains (97.2 to 194.4 mg.) of theophylline ethylenediamine three times a day is usually prescribed. From 2 to 3 grains (129.6 to 194.4 mg.) of theophylline three times a day, however, is frequently used, and it may be combined with theophylline ethylenediamine when a more pronounced diuretic action is desired. Occasionally in the cases of greater urgency, especially in the presence of nausea and vomiting, 480 mg. of theophylline ethylenediamine is administered intravenously once or twice daily.

15. Smith, Fred M.; Rathe, Herbert W., and Paul, W. D.: Observations on the Clinical Course of Coronary Artery Disease, *J. A. M. A.* **105**:2 (July 6) 1935.

RESULTS IN CASES OF CONGESTIVE FAILURE

The following reports of cases illustrate the action of the theophylline in the treatment of congestive failure due to disease of the coronary arteries. Digitalis was withheld, and only the cases of congestive failure in advanced stages were selected, in order to test the effectiveness of the medication.

CASE 1.—E. J., aged 67, was admitted to the University Hospital on Nov. 2, 1930, complaining of shortness of breath and swelling of the legs. Shortness of breath was first noticed in December 1929, and edema of the ankles in September 1930. The patient presented advanced congestive failure with marked orthopnea and cyanosis. The heart was very large, and the rhythm irregular, owing to auricular fibrillation. The blood pressure measured 140 systolic, and 90 diastolic.

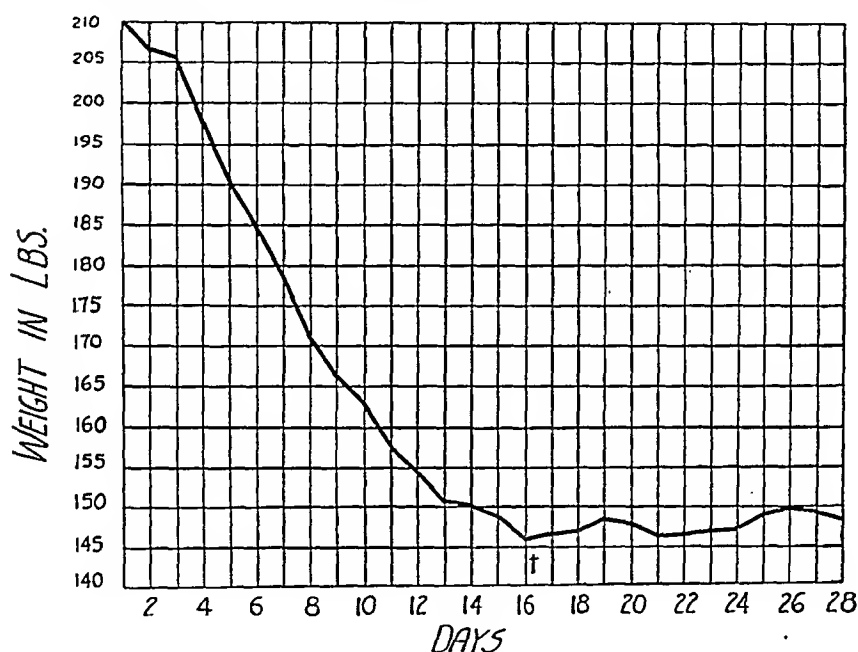


Chart 1 (case 1).—Curve showing the loss of weight after administration of theophylline in a case of congestive failure due to disease of the coronary arteries. The dagger indicates the point at which digitalis was prescribed.

Examination of the urine showed traces of albumin and occasional hyaline and granular casts. The teleoroentgenogram revealed that the transverse diameter of the heart measured 19 cm. and one pulmonary field, 14 cm. The electrocardiogram showed left axis deviation, auricular fibrillation, slurring of the ventricular complexes and an inverted T wave in lead 1.

The patient was given rest in bed, a cardiac diet, $\frac{1}{2}$ grain (32.4 mg.) of phenobarbital after meals and at bedtime, liquid petrolatum at night and in the morning, $\frac{1}{4}$ grain (16.2 mg.) of morphine sulfate hypodermically at bedtime, which was to be repeated if necessary to induce sleep but was discontinued after the third night, and 2 grains of theophylline three times a day. On the seventeenth day 15 minims (0.924 cc.) of tincture of digitalis three times a day was prescribed.

The curve in chart 1 shows the rapid loss in weight observed in this patient. It is to be noted that the weight decreased from 210 to 146 pounds (95.2 to

66.3 Kg.) in sixteen days. At this time digitalis was prescribed, and its administration was continued throughout the remainder of the stay in the hospital.

CASE 2.—Mrs. E. R., aged 66, was admitted to the University Hospital on May 9, 1930, because of congestive heart failure. She had been in the hospital in July 1929 for the same condition. The present attack began in March 1930. The patient presented the usual signs of advanced congestive failure. The heart was enlarged. The teleoroentgenogram revealed the transverse diameter of the heart to be 18 cm. and one pulmonary field, 13.1 cm. The blood pressure measured 145 systolic and 88 diastolic. The electrocardiogram showed slurred ventricular complexes of low amplitude and an iso-electric T wave in all the leads.

Treatment consisted of rest in bed, a cardiac diet, liquid petrolatum, $\frac{1}{2}$ grain (32.4 mg.) of phenobarbital after meals and at bedtime, and $\frac{1}{4}$ grain (16.2 mg.) of morphine sulfate given hypodermically at bedtime. There was no appreciable change in the condition of the patient for six days, except that

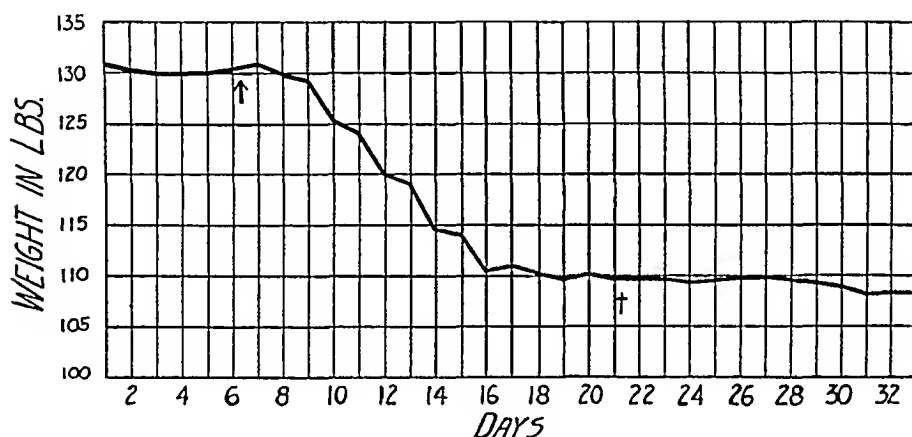


Chart 2 (case 2).—Curve showing the loss of weight after treatment with theophylline in a case of congestive failure. The arrow indicates the point at which the administration of theophylline was begun; the dagger, that at which the medication was supplemented by digitalis.

she was relaxed and slept well during the night. At this point 3 grains of theophylline three times a day was prescribed.

It is to be noted from the curve in chart 2 that the administration of theophylline was soon followed by loss in weight, which continued until the edema was entirely eliminated. This was accompanied by prompt improvement in the general condition of the patient. The treatment just outlined was supplemented by the use of digitalis on the twenty-first day.

CASE 3.—O. P., aged 58, was admitted to the University Hospital on Aug. 25, 1933, because of congestive failure and diabetes. There was a history of diabetes for twenty years. An attack of congestive failure occurred two years before, and there had been shortness of breath since that time. Ten days after admission a severe attack of substernal pain occurred, lasting several hours, followed by congestive failure.

The patient suffered from extreme dyspnea and presented extensive edema. The heart was moderately enlarged, both to the right and to the left. The teleoroentgenogram revealed that the transverse diameter of the heart measured 16 cm. and one pulmonary field, 14 cm. The urine contained albumin, sugar and

casts. The blood sugar content was 221 mg. per hundred cubic centimeters. The electrocardiogram showed ventricular complexes of low voltage and an inverted T wave in leads II and III.

The treatment consisted of rest in bed, a cardiac diet, 7 units of insulin three times a day, liquid petrolatum, $\frac{1}{4}$ grain (16.2 mg.) of morphine sulfate given hypodermically at bedtime and $1\frac{1}{2}$ grains of theophylline ethylenediamine three times a day. On the fifth day 2 grains of theophylline three times a day was added.

The curves for weight, vital capacity and venous pressure and the graph representing the output of urine are shown in chart 3. There was no significant change in any of these values until after administration of theophylline was begun, on the fifth day. It is to be noted that after this medication was begun the response was prompt.

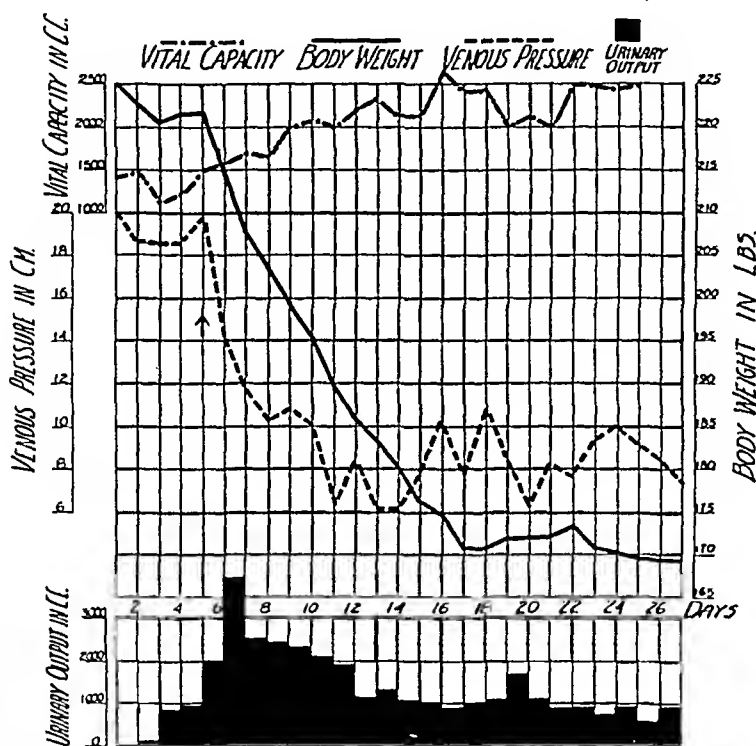


Chart 3 (case 3).—Curves for weight, vital capacity and venous pressure and a graph showing the output of urine in a case of congestive failure in which theophylline was used. The arrow indicates the point at which medication with theophylline ethylenediamine was begun.

CASE 4.—L. K., aged 64, was admitted to the University Hospital on Jan. 12, 1933, for the third time for the treatment of congestive failure. On each previous admission it had been difficult to restore the cardiac function, and during the second stay in the hospital salyrgan was finally administered to eliminate edema. The patient was again in a state of advanced cardiac failure. The heart was very large. The teleoroentgenogram revealed that the transverse diameter of the heart measured 20 cm. and one pulmonary field, 14 cm. The rhythm was irregular, owing to auricular fibrillation. The blood pressure measured 220 systolic and 130 diastolic. The electrocardiogram showed auricular fibrillation and an inverted T wave in leads I and II.

Treatment consisted of rest in bed, a cardiac diet, liquid petrolatum, morphine sulfate as necessary for sleep at night and 3 grains of theophylline ethylenediamine three times a day.

The curves for weight, venous pressure and vital capacity and the graph representing the output of urine are shown in chart 4. No appreciable change in any of these findings appeared until the seventh day. At this point appeared an increase in the output of urine, a reduction of 4 pounds (1.8 Kg.) in weight and increase in the vital capacity. On the eighth day venesection with the removal of 500 cc. of blood was performed. After this, there was a marked increase in the output of urine, accompanied by an abrupt reduction in weight and venous pressure and prompt improvement in the vital capacity.

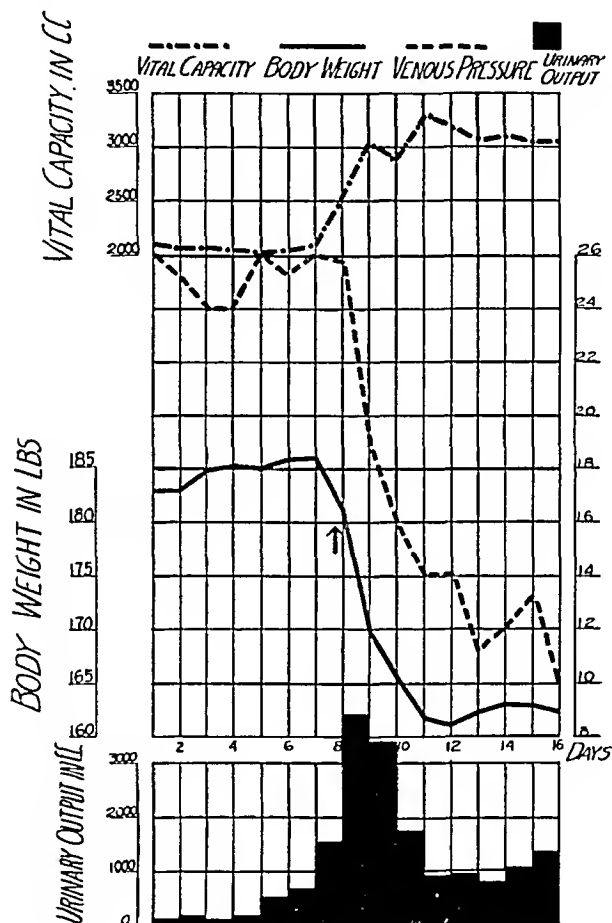


Chart 4 (case 4).—Curves for weight, vital capacity and venous pressure and a graph showing the output of urine in a case of congestive failure in which theophylline ethylenediamine was used. The arrow indicates the point at which a venesection was performed.

Comment.—The preparations of theophylline are among the most effective remedies in the treatment of congestive failure due to disease of the coronary arteries. The action is prompt and generally evident in all cases in which it is possible to restore the cardiac function, provided the work of the heart is reduced to the minimum through absolute rest in bed, relaxation and sleep. Occasionally, it may be necessary to increase the dosage, as illustrated in case 3. In the more advanced

forms of congestive failure the utilization of other available means of reducing the work of the heart, such as aspiration of excess fluid from the peritoneal and pleural cavities and venesection, may have a significant influence on the subsequent course, as shown in case 4.

In routine practice we usually prescribe digitalis in conjunction with theophylline ethylenediamine in the treatment of congestive failure resulting from disease of the coronary arteries. Digitalis is usually employed in the form of the powdered leaf, $1\frac{1}{2}$ grains from three to four times a day being given. After from three to five days the number of doses is reduced to one or two a day. When the patient is discharged from the hospital he is usually advised to continue the treatment with from 1 to $1\frac{1}{2}$ grains (64.8 to 97.2 mg.) daily. Occasionally, it may be necessary to increase the dosage if there is auricular fibrillation. The combination of digitalis in small amounts and theophylline is apparently more effective than either drug alone. We do not believe, however, that digitalis in large amounts is necessary, and it may even retard the progress. Certain of our patients have shown prompt improvement after the use of digitalis was discontinued and theophylline was prescribed.

Theophylline, generally in the form of theophylline ethylenediamine, $1\frac{1}{2}$ grains after meals, is continued after the patient leaves the hospital. This method of administration promotes the development of more efficient cardiac function and postpones the recurrence of symptoms. Patients, in reporting on their progress, have usually stated that they felt much better while on the medication, or on returning to the hospital because of recurrence of congestive failure they have often told us that they were free from symptoms during the time that they were taking theophylline ethylenediamine.

RESULTS IN CASES OF PAROXYSMAL DYSPNEA, ANGINA ON EFFORT AND OCCLUSION OF THE CORONARY ARTERIES

The results in 100 cases of paroxysmal dyspnea, angina on effort and occlusion of the coronary arteries in which treatment was administered outside the hospital are shown in the table. A large majority of the patients have been observed for more than one year, and some for three or four years. In all except a few instances theophylline was the only medicament employed for the cardiac disease. It was usually prescribed in doses of $1\frac{1}{2}$ grains three times a day, and was continued for a long period. The following cases are illustrative of those in which a favorable response was shown.

CASE 1.—Mrs. E. L. K., aged 68, was first examined on Aug. 4, 1932. She presented a history of shortness of breath and occasional angina on effort for two years. The angina had been more frequent and severe during the months prior to examination. The heart was slightly enlarged; there were no murmurs,

and the sounds were of good quality. The blood pressure measured 110 systolic and 88 diastolic. The electrocardiogram showed an S wave in lead I, a Q wave in lead III and notching of the QRS group.

The patient took theophylline for six weeks and obtained marked relief, and the medication was then discontinued. The symptoms returned in two weeks. She again took theophylline with resulting relief. She repeated this experience several times with the same results. She was last observed on April 5, 1933, and at the time of writing she was taking theophylline regularly.

CASE 2.—F. A. O., aged 71, was first examined on April 14, 1933. There was a history of shortness of breath on exertion and angina on effort for eight years. Occlusion of a coronary artery with progressive changes in the T wave occurred on April 12, 1933. The heart was enlarged, and the sounds were muffled. The blood pressure measured 128 systolic and 74 diastolic.

Rest in bed and theophylline were prescribed for eight weeks. The medication was discontinued after the patient was up and about. Dyspnea and angina returned, and the symptoms disappeared after resumption of medication. This patient also repeated the experience several times. During the past twelve months, however, he has taken theophylline regularly, and during this time he has been free from cardiac symptoms.

CASE 3.—J. G. P., aged 54, was first examined on April 25, 1933. There was a history of shortness of breath for several months. Shortly before examination

Results of Treatment with Theophylline in One Hundred Cases of Paroxysmal Dyspnea, Angina of Effort and Occlusion of the Coronary Arteries

	Number of Cases	Results		
		Favorable	Questionable	Negative
Paroxysmal dyspnea.....	20	13	2	5
Angina of effort.....	25	19	2	4
Occlusion of the coronary arteries.....	55	40	7	8
Total number of cases.....	110	72	11	17

the patient experienced several attacks of paroxysmal dyspnea, accompanied by a sense of substernal constriction. The heart was enlarged and a gallop rhythm was heard. The blood pressure measured 190 systolic and 120 diastolic. The electrocardiogram revealed bundle branch block. Theophylline was prescribed, and the patient was permitted to continue with the usual activities. He has received medication for one year and is free from symptoms.

CASE 4.—C. C. S., aged 65, was first examined on May 10, 1931. He gave a history of being short of breath on exertion for two years. For six months prior to examination he had had numerous attacks of paroxysmal dyspnea. The heart was enlarged, and gallop rhythm and a systolic apical murmur were noted. The blood pressure measured 150 systolic, and 80 diastolic. The electrocardiogram revealed bundle branch block.

After taking theophylline, the patient was able to be more active. He noticed that when medication was discontinued dyspnea returned. He has taken theophylline regularly for three years.

CASE 5.—L. B., aged 62, was first examined on May 9, 1931. He gave a history of occlusion of a coronary artery two months before, followed by shortness of breath on slight exertion. The heart was enlarged, and the cardiac sounds were of poor quality. The blood pressure measured 160 systolic and

110 diastolic. The electrocardiogram showed progressive changes in the T wave. Even though this patient continued work as a clerk, dyspnea disappeared after taking theophylline. He has been receiving medication for two years, and during this time he has not curtailed his activities.

CASE 6.—J. D. T., aged 61, was first examined on Jan. 10, 1933. There was a history of angina on effort for six months and occlusion of a coronary artery two months after the onset. The blood pressure measured 110 systolic, and 76 diastolic. The electrocardiogram showed the usual changes in the T wave. The patient was given rest in bed, and theophylline was prescribed for two months. Medication was discontinued on several occasions, and on each trial dyspnea returned but disappeared on the resumption of medication. The patient is now taking theophylline regularly.

CASE 7.—R. W., aged 64, was first examined on July 8, 1932. There was a history of occlusion of a coronary artery three months before and of shortness of breath and nocturnal dyspnea for six weeks. The heart was moderately enlarged, and the cardiac sounds were poorly differentiated. The blood pressure measured 122 systolic and 88 diastolic. The changes in the T wave suggested occlusion of a coronary artery.

The patient was treated with rest in bed and theophylline for six weeks. He was active and had no complaints eighteen months later. Recently he had nocturnal dyspnea. He is now taking theophylline and is free from symptoms.

CASE 8.—A. S. W., aged 58, was first examined on May 11, 1933. He had had occlusion of a coronary artery six months before, and three months prior to examination he began to experience angina on effort. The heart was enlarged, and a systolic apical murmur was heard. The blood pressure measured 122 systolic, and 88 diastolic. The electrocardiogram showed bundle branch block.

The angina was relieved by theophylline, and the patient resumed his regular activities. He discontinued the use of theophylline about three months ago, and dyspnea returned. Theophylline was again given and relief was obtained.

CASE 9.—W. C., aged 58, was first examined on Jan. 31, 1933. There was a history of occlusion of a coronary artery three years before and of shortness of breath on exertion since that time. Occlusion of a coronary artery again occurred seven weeks prior to examination, and two mild attacks of pain were experienced since. Shortness of breath appeared on slight exertion. The heart was enlarged, and the cardiac sounds were of poor quality. The blood pressure measured 190 systolic and 120 diastolic. There were progressive changes in the T wave.

The patient took theophylline regularly for one year. He then discontinued the medication and experienced shortness of breath, but on resumption of the drug the symptoms disappeared. He now carries on his regular activities and has shortness of breath only on unusual exertion.

CASE 10.—B. P., aged 55, was first examined on Dec. 3, 1932. He gave a history of epigastric pain on exertion for six years, which was relieved by rest. Occlusion of a coronary artery occurred two weeks prior to consultation, and there was a severe attack of pain again on the day of examination. The heart was moderately enlarged, and changes in the quality of the cardiac tones were noted.

Rest in bed and theophylline were prescribed for six weeks; then gradual extension of activities was permitted. On a few occasions medication was discontinued, and dyspnea returned. He has taken theophylline regularly for more than one year.

CASE 11.—L. K., aged 58, was first examined on Aug. 1, 1933. He gave a history of fatigability five years before with hypertension. He experienced shortness of breath during the preceding five years and attacks of nocturnal dyspnea during the month prior to examination. Substernal oppression was also present. The heart was moderately enlarged. The blood pressure measured 114 systolic and 70 diastolic. Changes were observed in the T wave.

Theophylline was prescribed, and the same activities were permitted as were usual before examination. The patient felt much improved and had no recurrence of dyspnea until six weeks prior to the time of writing, after he had been without theophylline for a month. He took theophylline again, and the symptoms disappeared. This experience was recently repeated.

CASE 12.—Mrs. O. F. B., aged 72, was first examined on Aug. 2, 1930. Weakness, angina on effort and dyspnea had been present for the preceding eighteen months. During the greater part of this time she had been taking digitalis but did not think that she had improved. Just prior to consultation, the angina had been more severe. The heart was enlarged; the cardiac tones were muffled, and a systolic apical murmur was apparent. The blood pressure measured 140 systolic and 100 diastolic. The electrocardiogram showed bundle branch block.

The patient showed marked improvement after taking theophylline. Later, digitalis was prescribed, and the patient thought that it promoted the return of the pain. She was without discomfort for two years.

CASE 13.—Mrs. S. W., aged 71, was first examined on Aug. 14, 1930. There was a history of two attacks of retrosternal pain during the preceding three years. The present attack was typical of that observed in association with occlusion of a coronary artery. The cardiac sounds were muffled, and a systolic murmur was heard at the apex. The blood pressure measured 140 systolic and 88 diastolic. There were progressive changes in the T wave.

The patient took theophylline regularly for two years and was comfortable. Medication was stopped for two weeks, and retrosternal heaviness was noted. She began to take theophylline again, and the discomfort disappeared. She is very active, but she has observed that if she discontinues the use of the drug for a time the heaviness in the chest returns. She is now taking the theophylline regularly and is free from symptoms.

CASE 14.—Mrs. A. W. B., aged 70, was first examined on May 28, 1931. Occlusion of a coronary artery had occurred six weeks before, followed by congestive failure. She had had severe attacks of nocturnal dyspnea one week prior to examination. The patient had been in the hospital and was receiving digitalis. The heart was moderately enlarged; the cardiac tones were distant and muffled, and the rate was moderately increased. The blood pressure measured 115 systolic and 75 diastolic. Râles were heard in the base of each lung, and the liver was engorged. The electrocardiogram showed negative T waves in leads I and II, with elevation of the RT segment.

The patient was advised to continue treatment with rest in bed, and $1\frac{1}{2}$ grains of theophylline ethylenediamine three times a day was added to the medication. She gradually improved. No further attacks of nocturnal dyspnea occurred. She has taken theophylline ethylenediamine regularly for several months. Now, three years later, she has no shortness of breath except on unusual exertion.

CASE 15.—W. H. McC., aged 63, was first examined on May 16, 1932. He had occlusion of a coronary artery in March 1932. He was in bed for four days and returned to work in six days. In a short time he began to have angina on effort. On May 10, 1932, a second attack of occlusion of

a coronary artery occurred. The pain was severe, and finally chloroform was administered for relief. The patient was short of breath. He remained in bed until May 15, 1932. The heart was slightly enlarged; the cardiac rate was 110; the tones were of poor quality, and there was a faint murmur. The blood pressure measured 105 systolic and 80 diastolic. Shortness of breath appeared on the slightest exertion. The patient was sent home to continue rest, and $1\frac{1}{2}$ grains of theophylline ethylenediamine three times a day was prescribed. He was observed at intervals of from three to four months until October 1933. His condition was then satisfactory. There was no angina on effort or shortness of breath, except on rather vigorous exercise. The patient continued to take theophylline and was still well two years after the onset of the cardiac disability.

CASE 16.—T. P. R., aged 60, was first examined on Feb. 19, 1925. Two weeks prior to examination he awakened with a feeling of fulness in the chest and difficulty in breathing. The feeling of heaviness lasted throughout the night. Since that experience he had had angina on effort and shortness of breath. The heart was slightly enlarged; the tones were distant, and no murmurs were heard. The blood pressure measured 90 systolic and 70 diastolic. The electrocardiogram showed suggestive changes in the T wave.

One and one-half grains of theophylline ethylenediamine three times a day was prescribed. The patient reported for a second examination two weeks later. No further angina was experienced. He returned again a year later and stated that he had been entirely free from cardiac symptoms. He attributed improvement to the use of theophylline.

CASE 17.—C. D., aged 58, was first examined in October 1929, while suffering an attack of occlusion of a coronary artery. The occlusion apparently involved a large vessel. A possible attack of occlusion had occurred in 1926. He had had angina on effort for several months; the heart was slightly enlarged, and the tones were of poor quality. The blood pressure measured 140 systolic and 90 diastolic. Characteristic changes were observed in the electrocardiogram.

The patient received rest in bed for four weeks and was then permitted gradually to get on his feet. Three grains of theophylline ethylenediamine three times a day was prescribed. The dose was later reduced to $1\frac{1}{2}$ grains three times a day. He has continued with this medication and is active and free from cardiac symptoms.

Comment.—The results in the aforementioned one hundred cases of paroxysmal dyspnea, angina on effort and occlusion of the coronary arteries are in general accord with what might be expected from the experimental study. It is to be noted that in a fairly large percentage favorable results were shown, and that in certain instances the change in the condition was striking. In the majority of the cases included in the group in which the results were questionable definite improvement was made, but when the variations in the course of the disease and other factors that might have a favorable influence on the disorder were excluded, the beneficial effects of the medication were doubtful. Finally, there were cases in which the results were definitely negative. Occasionally, an increase in the dose of theophylline brought about a distinct improvement in a patient for whom the results of the medication had been in doubt.

If one bears in mind the state of the coronary circulation generally presented in these conditions, it is not surprising that questionable results and failures are encountered. It is recognized from experimental and pathologic studies that much depends on the extent of the collateral circulation. It seems probable that the beneficial influence of theophylline is largely due to its action in promoting the development of this factor. If it is possible to develop and maintain an effective collateral circulation, theophylline is likely to be of value, but otherwise not. This may require time, and therefore the necessity of continuing the medication for a long period is evident. The importance of the continued use of the theophylline is well illustrated by certain cases already described.

We have been favorably impressed with the results of the use of theophylline in the treatment of acute occlusion of the coronary arteries. It should be recalled that in a number of cases cited the patients were first observed during or soon after occlusion of a coronary artery, the patients of the latter group usually coming for examination because of paroxysmal dyspnea, angina on effort or congestive failure. One of the 4 patients (case 3) who presented congestive failure had occlusion of a coronary artery ten days before admission to the hospital. While the response to theophylline may be prompt, even in cases in which the patient is not under observation for some time after the development of infarction, we believe that more lasting results are obtained when the medication is employed in the early stages of occlusion of a coronary artery.

CONCLUSION

It is important that measures be directed toward the restoration and maintenance of an efficient coronary circulation in the treatment of disease of the coronary arteries. The preparations of theophylline have a marked dilating action on the coronary vessels in the experimental animal, and clinical experience has demonstrated that they are valuable therapeutic agents in the treatment of disease of the coronary arteries, regardless of whether the cardiac disability is expressed by congestive failure, paroxysmal dyspnea, angina on effort or occlusion of the coronary arteries. Questionable results and failures are encountered, but this is to be expected in the more advanced forms of the disease. Theophylline should be prescribed as soon as the diagnosis of disease of the coronary arteries is established, and its administration should be continued for a long period, in order to insure the maximum benefit from the medication. It should be remembered, however, that this constitutes only one measure in the treatment and, except for experimental purposes, should not be employed to the exclusion of other established means of restoring the cardiac function.

CARBOHYDRATE INTOLERANCE AND INTESTINAL FLORA

I. A CLINICAL STUDY BASED ON SIXTY CASES

T. L. ALTHAUSEN, M.D.

J. B. GUNNISON, M.A.

M. S. MARSHALL, PH.D.

AND

S. J. SHIPMAN, M.D.

SAN FRANCISCO

Intestinal intolerance of carbohydrate with symptoms centering around marked meteorism is a rather common condition, the significance of which is often not appreciated. This symptom complex was first described by Schmidt and Strasburger¹ in 1901 in Germany and by Herter² in 1907 in this country. In the recent English medical literature the only publications on this subject have been by Kendall³ and Hurst and Knott.⁴ Textbooks usually ignore this condition.

In our gastro-intestinal clinic, during the past five years, in 9 per cent of the cases the major diagnosis was intestinal intolerance of carbohydrate. This figure exaggerates the frequency of the condition among patients with conditions related to the digestive tract, as a disproportionately large number of patients with obscure conditions are referred to this clinic for diagnosis, but it indicates that this syndrome is fairly common.

From the Department of Medicine and the Department of Bacteriology, University of California Medical School.

Read at the thirty-sixth annual meeting of the American Gastro-Enterological Association, Washington, D. C., May 8, 1933, and before the General Medicine Section of the California Medical Association at the sixty-third annual session, Riverside, May 3, 1934.

1. Schmidt, A., and Strasburger, J.: Experimentelle und klinische Untersuchungen über Functionsprüfung des Darmes: VI. Ueber die intestinale Gährungs-dyspepsie der Erwachsenen, *Deutsches Arch. f. klin. Med.* **69**:570, 1901.

2. Herter, C. A.: The Influence of Food and of Epithelial Atrophy on the Manifestations of Saccharo-Butyric Intestinal Putrefaction, *J. A. M. A.* **49**:1965 (Dec. 14); 2077 (Dec. 21) 1907.

3. Kendall, A. I.: Intestinal Intolerance for Carbohydrate, Associated with Overgrowth of Gas Bacillus (*Bacillus Welchii*), *J. A. M. A.* **86**:737 (March 11) 1926.

4. Hurst, A. F., and Knott, F. A.: Intestinal Carbohydrate Dyspepsia, *Quart. J. Med.* **24**:171, 1931.

CLINICAL PICTURE

From a survey of fifty consecutive cases we find that this disease occurs in females four times as often as it does in males. About 60 per cent of our patients at the time of observation were between the ages of 30 and 50 years. Few were younger. On the other hand, the onset of symptoms in two thirds of the cases occurred between the ages of 20 and 40 years. The shortest duration of symptoms was six

TABLE 1.—*Frequency of Gastro-Intestinal Symptoms in Fifty Cases of Intestinal Intolerance of Carbohydrate*

Symptoms	Percentage
Meteorism.....	100
Abdominal pain.....	84
Nocturnal distress.....	70
Excessive flatus.....	74
Belching.....	76
Constipation.....	82
Diarrhea (periodic or chronic).....	28
Mucus in stools.....	30
Periodic digestive upsets.....	60
Conscious intolerance of carbohydrate.....	68

TABLE 2.—*Incidence of Systemic Manifestations in Fifty Cases of Intestinal Intolerance of Carbohydrate*

Systemic Manifestations	Percentage
Asthenia.....	98
Nervousness.....	88
Vasomotor instability.....	80
Blood pressure:	
Hypotension.....	38
Normal.....	58
Hypertension.....	4
Gastric acidity:	
Achlorhydria.....	14
Hypochlorhydria.....	52
Normal.....	28
Hyperchlorhydria.....	6
Anemia.....	40
Albuminuria.....	6
Chronic choroidoretinitis.....	24
Cardiac consciousness.....	52

weeks; the longest, twenty-three years; the average was more than four years.

The incidence of the various findings in our cases is shown in tables 1 and 2. Flatulence was marked in all the patients. Abdominal distress ranged from a sense of pressure to pain of a dull or colicky nature and was present in four of five cases. Flatus in excessive amounts was almost as common and, as a rule, was relatively odorless. Belching, another frequent symptom, was very annoying in some cases. Waking during the night due to abdominal distress, when present, is almost pathognomonic of this condition. It occurred most frequently between midnight and 3 o'clock in the morning. Patients are usually able to

control their nocturnal distress by walking around, massaging the abdomen or taking a warm drink and, finally, after passing some gas, fall asleep again.

Many patients suspect a relationship between the ingestion of certain carbohydrate foods and the exacerbation of symptoms, while from others this information is elicited only by careful questioning. The latter is not surprising, because starches in some form are part of every meal. Most frequently the offending article of food is the potato, but many patients also have a great deal of trouble with milk. Dried beans, peas and lentils are rarely mentioned by patients, because most of them have learned long ago to avoid them altogether. Three patients in this series named candy and sugar as the worst offenders. The intensity of symptoms is not uniform but rather is characterized by intermittent exacerbations which, in more than half of the cases, assume the proportions of an attack lasting for several days.

Constipation was present in most cases. Among the more severe cases periodic attacks of diarrhea or habitual looseness of the bowel was the rule. In about half of the patients having periodic diarrhea the condition could be classified as mucous colitis. Fifteen per cent of our patients had increased amounts of mucus in their stools without diarrhea. The feces in this condition are normal or light in color, usually acid to litmus and often show many bubbles of gas. Microscopic examination after the addition of compound solution of iodine U. S. P. reveals in most cases blue-staining granules of starch, but these are also frequently found in normal specimens. On the whole, examinations of the stool yield no information of great diagnostic value. The presence of much mucus has an unfavorable prognostic significance.

Two thirds of all the patients had diminution or absence of free hydrochloric acid in the stomach. Roentgenologic studies of the colon were carried out in thirty patients but showed no consistent abnormalities. In many cases dilatation of the colon was observed. Other patients had minor abnormalities such as ptosis, spasticity or redundancy. In a number of patients tenderness along the course of the large bowel was noticed.

Turning to symptoms outside of the digestive tract, asthenia and nervousness were prominent, in point of both frequency and severity. Vasomotor instability in varying degrees, sometimes with dizziness, sometimes with severe frequent headaches, was also an important characteristic in most cases. In addition, five patients suffered from a mild form of Raynaud's disease.

More than one half of the patients complained of palpitation and extrasystoles. The blood pressure was found to be normal in a majority and low in a considerable proportion of cases. Even mild hypertension was rare. About one fourth of our patients were found to have chronic

choroidoretinitis, sometimes with impairment of sight. Anemia with less than 80 per cent hemoglobin and a red blood cell count under 4,200,000 was present in 40 per cent of our cases.

The urine of almost all the patients was normal. An important exception was presented in a group of instances collected by one of us (S. J. S.) because of pronounced intolerance to starches combined with multiple toxic symptoms. Albuminuria was invariably among the latter. Occasionally hematuria and cylindruria were also present, without other evidence of nephritis. The clinical features of these cases are summarized separately in tables 3 and 4.

TABLE 3.—*Frequency of Gastro-Intestinal Symptoms in Ten Cases of Intestinal Intolerance of Carbohydrate with Toxic Signs*

Symptoms	Percentage
Meteorism.....	100
Abdominal pain.....	100
Nocturnal distress.....	50
Excessive flatus.....	100
Constipation.....	...
Chronic diarrhea.....	100
Mucus in stools.....	50
Periodic digestive upsets.....	80
Conscious intolerance of carbohydrate.....	100

TABLE 4.—*Incidence of Systemic Manifestations in Ten Cases of Intestinal Intolerance of Carbohydrate with Toxic Signs*

Systemic Manifestations	Percentage
Asthenia.....	100
Nervousness.....	100
Vasomotor instability.....	100
Blood pressure:	
Hypotension.....	...
Normal.....	67
Hypertension.....	33
Anemia.....	90
Urinary findings:	
Albuminuria.....	100
Hematuria.....	20
Cylindruria.....	20
Chronic choroidoretinitis.....	40
Extrasystoles.....	100

Persons suffering from intestinal intolerance of carbohydrate are, as a rule, very unhappy and often become incapacitated, especially during the periodic exacerbations to which they are subject. One is struck by the faithfulness with which these patients, most of whom have undergone many types of unsuccessful therapy, follow rigid dietary restrictions and by the great length to which they go in order to secure competent medical advice.

ETIOLOGY AND PATHOGENESIS OF SYMPTOMS

1. *Local Gastro-Intestinal Manifestations.*—The flatulence in intestinal intolerance of carbohydrate is real, as is shown by the prominence

which the passage of large amounts of flatus occupies among the complaints. This was substantiated by the finding of abdominal distention and palpable gas, especially in the region of the cecum and of the splenic flexure. Having established an undue accumulation of gas, one must decide whether it is caused by excessive production of gas in the intestine or by interference with absorption of normally formed gases into the blood preparatory to their elimination through the lungs.

At the beginning of this investigation, on the basis of reports in the literature, a positive outcome of fermentation tests ⁵ was accepted as proof of excessive production of gas in the colon. Later a critical investigation into the significance of these tests forced us to the conclusion that they are worthless, at least from the clinical standpoint. This opinion is supported by the experience of other workers ⁶ that stormy fermentation can be produced by stools of persons without flatulence.

There are several possible causes of increased intestinal fermentation to be considered. Herter ⁷ and, later, Kendall ⁸ suggested as a cause changes in the intestinal flora, chiefly an overgrowth of *Clostridium Welchii*, made possible by reduction in the activity or number of lactic acid organisms. Kendall further strengthened this opinion by showing that dietary measures restraining the activity of these microbes are of therapeutic value in intolerance of carbohydrate. Similarly, Simonds ⁹ and Torrey ¹⁰ see in stormy fermentation proof of a predominance of the Welch organism in the stool.

In conflict with this view are the results of our own quantitative studies of *Cl. Welchii*, which demonstrated that even extreme degrees of stormy fermentation may occur with only small numbers of this micro-organism in the stools. Moreover, contrary to the hypothesis of Herter, no consistent correlation could be made between numbers of the Welch bacillus in the fecal flora and intolerance of carbohydrate. Some

5. Details of the bacteriologic studies are given in the second paper of this series.

6. MacNeal, W. J.; Latzer, L. L., and Kerr, J. E.: The 'Fecal Bacteria of Healthy Men, *J. Infect. Dis.* **6**:571, 1909. Hewes, H. F., and Kendall, A. I.: The Gas Bacillus as an Agent of Intestinal Fermentation and Diarrhea, Boston M. & S. J. **166**:75, 1912. Schmidt and Strasburger.¹

7. Herter, C. A.: The Common Bacterial Infections of the Digestive Tract and the Intoxications Arising from Them, New York, The Macmillan Company, 1907, p. 291.

8. Kendall, A. I.: Hypotension, *Illinois M. J.* **56**:404, 1929; footnote 3.

9. Simonds, J. P.: Studies in *Bacillus Welchii* with Special Reference to Classification and to Its Relation to Diarrhea, Monogr. 5, Rockefeller Institute for Medical Research, 1915.

10. Torrey, J. C.: The Fecal Flora of Typhoid Fever and Its Reaction to Various Diets, *J. Infect. Dis.* **16**:72, 1915.

patients with this condition had very large numbers of the Welch organism, while others had but a few. The most consistent overgrowth of *Cl. Welchii* was found in a small group of patients with hypochromic anemia and achlorhydria. The same wide and unaccountable variations were found in the number of aciduric organisms. Similarly, no definite relationship could be found between clinical features in different cases and the amount of putrefaction or the presence of various types of streptococci and of hemolytic *Bacillus coli* in the stools. In practically all the cases the flora was moderately proteolytic.

A second possibility which could account for the increased production of gas is the upward extension of the colonic flora into regions of the ileum and jejunum, where absorption of carbohydrates normally takes place in almost complete absence of bacteria. The opportunities for greatly increased fermentation under such conditions are obvious, even in the absence of qualitative changes in the bacterial flora.

The fecal flora is normally restrained from growing above the lower ileum by the hydrogen ion concentration of the small intestine, which is dependent on normal gastric secretory function.¹¹ In achlorhydria, Arnold and Brody,¹² Knott¹³ and others found the colonic flora extending into the jejunum and even into the duodenum. Porges and Essen¹⁴ reported in some cases of fermentative diarrhea infestation of the ileum by starch-fermenting bacteria. In addition, Herter,¹⁵ Bogendörfer¹⁶ and Kendall and Schmitt¹⁷ demonstrated an extension of *Cl. Welchii* into the small intestine of patients with absence or diminution of gastric acidity. A better understanding of the mechanism of such a bacterial invasion of the small intestine from below can be gained from Nechoroschew's¹⁸ description of cyclic variations in the

11. Arnold, L., and Brody, L.: The Gastro-Duodenal Bactericidal Mechanism, *Am. J. Hyg.* **6**:672, 1926.

12. Arnold, L., and Brody, L.: Bacterial Flora and Hydrogen Ion Concentration of Duodenum, *J. Infect. Dis.* **38**:249, 1926.

13. Knott, K. A.: Addison's Anemia and Subacute Combined Degeneration of the Cord; Rôle of Achlorhydria and Intestinal Infection, *Guy's Hosp. Rep.* **77**:1, 1927.

14. Porges, O., and Essen, H.: Ueber die Pathogenese und Therapie der sogenannten dyspeptischen Diarrhöen, *Ztschr. f. klin. Med.* **109**:12, 1928.

15. Herter, C. A.: On Bacterial Processes in the Intestinal Tract in Some Cases of Advanced Anemia, with Especial Reference to Infection with *B. Aerogenes Capsulatus* (*B. Welchii*), *J. Biol. Chem.* **2**:1, 1906.

16. Bogendörfer, L.: Ueber die Flora des menschlichen Dünndarmes, *Deutsches Arch. f. klin. Med.* **140**:257, 1922.

17. Kendall, A. I., and Schmitt, F. O.: Physiologic Action of Certain Cultures of the Gas *Bacillus*, *J. Infect. Dis.* **39**:250, 1926.

18. Nechoroschew, N. P.: Periodische Tätigkeit des Verdauungskanal und Darmflora, *Ztschr. f. d. ges. exper. Med.* **66**:10, 1929.

duodenal flora of dogs. He found that during periods of rest the duodenal flora gradually increased, to reach its maximum just before a period of activity (as shown by balloons placed in the intestine). During periods of activity acid waves from the stomach forced the flora to retreat and sterilized the duodenum. Since the majority of our patients were found to have a decrease or absence of hydrochloric acid in the stomach, and since Herter² and Kendall³ also reported the frequent occurrence of hypochlorhydria in intolerance of carbohydrate, conditions in this syndrome must be favorable for an invasion of the small intestine by colonic organisms.

Of great interest in this connection is the work of Arnold,¹⁹ indicating that alterations in the equilibrium of the autonomic nervous system, especially any changes in the heat-regulatory mechanism, may inhibit the normal bactericidal power of the small intestine, allowing the fecal flora to ascend into the upper part of the alimentary tract. The phenomena of vasomotor instability in 80 per cent of our patients, which has already been mentioned and which was also noticed by Herter,² may in this light constitute an important factor in facilitating an upward extension of the intestinal flora. Of further significance is the fact that potatoes, beans and root vegetables, as a rule, are more troublesome to patients than bread and macaroni. In the former the starch is enclosed in cellulose envelops of varying thickness²⁰ and therefore is not readily absorbed, reaching the lower part of the ileum. In the latter foodstuffs the starch is freed from its cellulose covering by milling and is absorbed higher in the small intestine. It may seem surprising that milled starches and sugar should cause any intestinal fermentation at all, a fact also noticed by Herter² and Kendall.³ However, there is evidence that white bread and saccharose, if taken in large amounts, may reach the cecum.²¹ Also, the fecal flora can, in some cases, extend as high up as the duodenum. The marked intolerance of our patients to lactose, which is absorbed so slowly that when fed in large amounts it may even be detected in the stools,²² is probably to be explained on the same basis.

One of our cases illustrates well what may happen when a fecal flora establishes itself in the ileum. A woman, aged 30, who four years

19. Arnold, L.: The Passage of Living Bacteria Through the Wall of the Intestine and the Influence of Diet and Climate upon Intestinal Autoinfection, *Am. J. Hyg.* **8**:604, 1928.

20. Strauss, L.: Verdauung von Stärke aus geschlossenen Zellen, *Arch. f. Verdauungsk.* **41**:11, 1927.

21. Torrey, J. C.: The Regulation of the Intestinal Flora of Dogs Through Diet, *J. M. Research* **39**:415, 1918.

22. Hull, T. G., and Rettger, L.: The Influence of Milk and Carbohydrate Feeding on the Character of the Intestinal Flora, *J. Bact.* **2**:47, 1917.

previously had undergone removal of the colon for multiple polyposis, entered the University of California Hospital complaining of symptoms related to a severe degree of intolerance for carbohydrates. On investigation, the lower part of the ileum was found to have assumed some of the characteristics of the colon. Part of the time the patient passed soft but formed stools through the ileostomy opening, showing that considerable dehydration of the intestinal contents took place. Haustral markings were demonstrable in the ileum at the beginning of a barium sulphate enema but were later obliterated by greater filling of the bowel. Finally an atypical fecal flora with predominance of yeasts, streptococci and *Cl. Welchii* was found in the stools. The passage of much mucus, the absence of free hydrochloric acid in the gastric contents during fasting and failure to obtain relief from treatment were also important features of this case.

The third possible cause for increased fermentation lies in the penetration of abnormally large amounts of sugar or starch into the colon. Rapid passage of chyme through the small intestine could produce this. Porges and Essen¹⁴ observed increased motility of the small intestine roentgenologically in a certain proportion of persons suffering from "fermentative diarrhea." In one of their cases barium sulphate appeared in the rectum two hours after it was given by mouth. Moreover, these observers were able to bring about a disappearance of undigested starch from the stools of these patients by the administration of opium. At least one of our patients also had intestinal hypermotility, as charcoal used to appear in his stools about six hours after ingestion. Porges and Essen quote an ingenious explanation of the origin of fermentative diarrhea from Schmidt and von Noorden's book²³ to the effect that products of fermentation accelerate the emptying of an abnormally sensitive colon and reflexly bring about hypermotility of the small intestine, which sends increased amounts of undigested starch into the colon, thereby still further increasing fermentation. On the other hand, increased motility of the small intestine might be due directly to the formation of butyric and other irritating acids by fermentation within its lumen.

Carbohydrate foods, especially starch in unruptured vegetable cells, when eaten in excess, might prove to be beyond a person's capacity to digest and to absorb during passage through the small intestine. A suggestive case of this nature came to our attention when a woman suffering from intolerance of carbohydrate consulted us about her son, aged 10, whom she had been "stuffing with starchy foods" in

23. Schmidt, A., and von Noorden, C. H.: *Darmkrankheiten*, Munich, J. F. Bergmann, 1921; quoted from Herter.¹⁵

an attempt to increase his weight. The child had most of the intestinal but none of the systemic manifestations of intolerance for carbohydrates. He was cured by merely being put on a reasonable diet.

Hurst and Knott⁴ attributed excessive fermentation in patients with this syndrome to failure of digestion of unruptured granules of starch in the small intestine due to an insufficiency of ferments caused by previous enteritis. Their explanation involves the combination of an insufficiency of a hypothetic amylolytic ferment in the succus entericus with continued activity of an as yet undemonstrated diastase secreted in the cecum. In addition, the authors claimed that intestinal intolerance of carbohydrate does not occur in the presence of achlorhydria, because in the absence of hydrochloric acid digestion of starches is completed by the unchecked action of salivary ptyalin in addition to that of pancreatic amyllopsin. The first part of this theory appears to us speculative,^{23a} and the second part is contradicted by our experience with seven patients who had intolerance for carbohydrates in the presence of achlorhydria. Moreover, this explanation does not account for the occasional patients who have less tolerance for sugar than for starches. Finally, in contrast to Hurst and Knott, we were able to elicit a history of previous infection in the small bowel (mainly typhoid fever) in only five of our cases. Faulty digestion or poor absorption of carbohydrates in the small intestine without abnormal motility theoretically may account for the fact that excessive amounts of starch reach the colon, but so far no cases have come to our attention in which there was evidence in favor of either of these conditions.

There are persons who have no flatulence and yet consistently pass stools which contain enormous numbers of *Cl. Welchii* and other fermentative organisms. Since some of these persons also have achlorhydria and therefore conditions favorable for an upward extension of the fecal flora and yet deny bloating, one is compelled to search for factors other than mere increase in intestinal fermentation in order to explain the symptom complex of intolerance for carbohydrates. Such a factor one finds in interference with the absorption of gases from the intestinal lumen. In discussing the importance of various conditions contributing to the production of flatulence, Alvarez²⁴ writes: "Even

23a. Since this was written, Dr. W. H. Owles, at the Thorndike Memorial Laboratory in Boston, found by direct examination of normal persons "a completely insignificant production of diastase in the small intestine" which he was "unable to increase to a significant value by any means (food by mouth, locally, etc.)." Dr. Owles also investigated the case of one patient with intestinal intolerance to carbohydrate who had "high normal pancreatic diastase." (Personal communication to the authors.)

24. Alvarez, W. C.: *The Mechanics of the Digestive Tract*, New York, Paul B. Hoeber, Inc., 1928, chap. 26, p. 347.

when fermentation is active, other factors must enter in before the patient can be annoyed by flatulence, because normally so much of the gas is promptly taken up by the blood and excreted by the lungs." Then he proceeds to enumerate several factors favoring flatulence and assigns an important place to interference with the intestinal absorption of gases and to changes in the intestinal circulation. Schoen,²⁵ who did some excellent experimental work on the diffusion and resorption of intestinal gases under physiologic and pathologic conditions, went even further, stating that interference with the resorption of gases is a more important cause of flatulence than the excessive production of gases.

Schoen considered a loss of tonus by the intestinal musculature the most important factor interfering with the absorption of gases and supported his view by showing that pilocarpine increases and atropine markedly diminishes the resorption of gas from the intestine. These findings may have an important bearing on our clinical syndrome, because asthenia with weakness of the abdominal wall and consequent low intra-abdominal pressure was a constant finding in our patients. Schmidt and Strasburger,¹ Herter² and Kendall³ also commented on the asthenia and low physical endurance common to their patients with intolerance of carbohydrate. Excessive distention of the intestine by gas and the paralyzing effects of some intestinal toxins, especially those of the amine group, on the smooth musculature of the bowel were considered by Schoen additional factors interfering with the intestinal absorption of gases. We have already pointed out that excessive gaseous distention is a constant complaint among our patients. The formation of toxic substances in the bowel is also possible and will be considered later.

Schoen suggested that another factor decreasing the absorption of gases may be interference with the intestinal circulation by excessive distention. Van Zwalenburg²⁶ and Dragstedt, Lang and Millet²⁷ furnished quantitative data on this subject. The former author showed that an intra-intestinal pressure of 30 mm. of mercury begins to slow the blood flow of the intestine, while a pressure of 130 mm. stops it entirely. The latter investigators found that the duodenum, jejunum and ileum were sensitive to increases in intestinal pressure in that order; that a pressure of 20 mm. of mercury had a noticeable effect, and that an intrajejunal pressure of 80 mm. of mercury reduced the

25. Schoen, R.: Experimentelle Untersuchungen über den Meteorismus, *Deutsches Arch. f. klin. Med.* **147**:224, 1925; **148**:86, 1925.

26. Van Zwalenburg, C.: Strangulation Resulting from Distention of Hollow Viscera, *Am. J. Surg.* **46**:780, 1907.

27. Dragstedt, C. A.; Lang, V. F., and Millet, R. F.: The Relative Effects of Distention on Different Portions of the Intestine, *Arch. Surg.* **18**:2257 (June) 1929.

jejunal blood flow by about 60 per cent. Vasomotor relaxation due to nervousness or to the action of toxins on the smooth muscle fibers of the blood vessels may be another contributing cause. Alvarez stated that "the flatulence of nervous persons might be due at least in part to upsets in the gas exchange of the bowel, associated with an internal blushing and blanching similar to that which takes place so commonly in the skin." As shown in tables 2 and 4, almost all our patients were nervous, and, in addition, a great majority had vasomotor instability. Similar findings for this syndrome were reported by other medical writers.

What gas or gases are responsible for flatulence in intestinal fermentation? Six gases commonly present in the intestine must be considered.²⁸ Oxygen is usually found only in amounts under 1 per cent and is readily utilized by bacteria and absorbed into the blood. The nitrogen content of the intestinal gas varies from 10 to 60 per cent. This gas comes from the air, and there is practically no absorption of it from the intestine even under most favorable conditions. Methane may be present in the intestine to the extent of 50 per cent. Its formation is favored by a diet of legumes and, to a lesser degree, by a diet rich in meat. Little of this gas is found in persons on a milk diet. Hardly any methane is produced by the fermentation of starch and sugars, and only minimal amounts of it are resorbed, even by the normal intestine. It is, therefore, clear that the decreased absorption of gases would not appreciably increase the amount of oxygen, nitrogen or methane in the bowel. Hydrogen sulphide probably also plays little or no part in most cases of intestinal intolerance for carbohydrates, as shown by the relatively odorless nature of the flatus.

There is usually less than 5 per cent of uncombined hydrogen in the intestinal gas of a normal person on a mixed diet, but this proportion may rise to as high as 55 per cent in persons on a milk diet. Since from two thirds to three fourths of gas arising from the fermentation of carbohydrates is hydrogen, and since even normally it is absorbed from the intestine to only a moderate degree, the importance of this gas for the production of flatulence in patients with increased intestinal fermentation is at once apparent.

Carbon dioxide is represented in the flatus of normal persons to the extent of from 5 to 40 per cent. From one fourth to one third of the gas evolved by the fermentation of carbohydrate is carbon dioxide.

28. Ruge, E.: Beiträge zur Kenntnis der Darmgase, *Chem. Centralbl.-Bl.* **7**:347 and 353, 1862. Fries, J. A.: Intestinal Gases of Man, *Am. J. Physiol.* **16**:468, 1906. Bokai, A.: Experimentelle Beiträge zur Kenntnis der Darmbewegungen, *Arch. f. exper. Path. u. Pharmakol.* **23**:207, 1887. Simonds.⁹ Alvarez.²⁴ Schoen.²⁵

Since this gas is resorbed three times as rapidly as the next most absorbable gas, any interference with the resorption of gases from the intestine is particularly apt to cause flatulence due to the accumulation of carbon dioxide. In addition, carbon dioxide, in contrast to oxygen, nitrogen and hydrogen, has been shown to have also a chemically irritating action on the bowel.

In concluding this survey of possible causes of flatulence in intestinal intolerance of carbohydrate, the conclusion seems inescapable that in every patient several factors favoring increased fermentation and interfering with resorption are operative in bringing about the accumulation of gases in the bowel, and that in various cases different factors may be in the foreground. The relative importance of excessive fermentation and decreased absorption of gases in the production of meteorism in individual cases of this condition might be learned from the relative proportions of hydrogen and carbon dioxide in the flatus. To date there are no analyses of intestinal gases in this condition on record.

Constipation, when present, may be of contributory significance in the genesis of meteorism, because stagnation of intestinal contents is recognized as favoring flatulence.¹³ On the other hand, according to Zinsser,²⁹ the abnormal splitting of carbohydrates, with the production of butyric and other organic acids, in itself results in hyperacidity which may cause stasis of the bowel. In fact, constipation is a common symptom in patients with intolerance of carbohydrate. In cases in which organic acids are produced in larger amounts diarrhea in periodic attacks appears and finally may become chronic in severe cases. Bokai³⁰ substantiated this experimentally by injecting organic acids formed by the fermentation of sugars into the bowel and producing diarrhea. The irritating action of carbon dioxide may contribute both to early constipation and to late diarrhea.

The abdominal distress and waking at night are probably due mainly to gaseous distention, because the passage of flatus is always accompanied by at least partial relief. Intestinal spasm from irritating products of fermentation may also be a source of pain in the abdomen.

Increased amounts of mucus, which is present in the stools in the more severe cases, confirm the existence of chronic intestinal irritation. Simonds⁹ and especially Sittler³¹ consider the mucous covering of the intestine a favorite habitat of *Cl. Welchii*, even in normal persons. We also noticed that in patients with much mucus in the stools the condition

29. Zinsser, H.: *A Text Book of Bacteriology*, New York, D. Appleton & Company, 1923, p. 227.

30. Bokai, A.: *Experimentelle Beiträge zur Kenntnis der Darmbewegungen*, Arch. f. exper. Path. u. Pharmakol. 24:151, 1887.

31. Sittler, P.: *Die wichtigsten Bakterientypen der Darmflora beim Säugling*, Würzburg, C. Kabitzsch, 1909; cited by Kendall.⁶

was often refractory to treatment. Porges and Essen¹⁴ made similar observations in cases of fermentative diarrhea. It is possible that an excess of mucus offers a specially good soil for spore-forming, carbohydrate-fermenting anaerobes, or that it in some way protects these organisms against therapeutic measures.

Belching may be a disagreeable feature, especially to the fastidious patient. In some cases it is doubtless due to the swallowing of air in an effort to relieve the feeling of distention which the patient attributes to the presence of gas in the stomach. On the other hand, there are patients, particularly those having single large eructations spaced at considerable intervals, in whom gases formed probably in the upper part of the small intestine collect in the stomach. This can be determined by placing a cork between the teeth to prevent the swallowing of air or by analysis of the eructated gas.

2. *Systemic Manifestations*.—Among the complaints of patients with intestinal intolerance of carbohydrate is a train of symptoms consisting of marked asthenia, fatigability, nervousness and vasomotor instability. To these are often added frequent severe headaches, hypotension and hypochlorhydria. Patients in the group with toxic symptoms also emphasize mental symptoms variously described as "feeling fagged," "unable to think clearly," etc. The origin of these symptoms, which collectively represent a state typical for patients with intolerance of carbohydrate, is not entirely clear. However, it probably will not be far from the truth to interpret them as the constitutional background of persons who fall victims to this condition. An overlay created by several years of chronic distress and possibly, in a small number of cases, also by the absorption of toxic substances from the intestine, intensifies these constitutional characteristics.

The enumerated symptoms are not due to constipation, because practically all "constipated" patients in this series kept their bowels open by daily catharsis, while in the more severe cases there were at least two or three spontaneous loose stools a day. An analysis of coexisting diseases in these patients occasionally permitted us to account for some general symptoms on the basis of focal infection, postmenopausal ovarian insufficiency, arteriosclerosis and other conditions, but was never sufficient to explain the whole clinical picture.

Of great theoretical and practical importance among the systemic manifestations of this syndrome are anemia, albuminuria and chronic choroidoretinitis, because we feel justified in ascribing them to the absorption of toxic substances from the intestine. Anemia was present in 40 per cent of the fifty consecutive cases. Anemia was more frequent and more severe among patients selected for the presence of toxic symptoms. Of ten cases in this group, in one the blood was normal; in

another case the erythrocytes numbered 4,240,000, and in eight cases the red blood cells ranged between 2,710,000 and 3,860,000. After these patients were put on a diet low in starches their blood, without exception, showed a gradual rise of erythrocytes to a normal level of at least 4,500,000 and, in most cases, even higher. Anemia in cases of intolerance for carbohydrates had been previously noticed by Schmidt and Strasburger¹ and was emphasized by Herter.¹⁵

An extensive literature linking different types of anemia with the intestinal absorption of toxic substances is ably reviewed by Moench, Kahn and Torrey³² and by van der Reis.³³ However, these reviews do not mention the recently much discussed hypochromic anemia, which in many respects bears a striking resemblance to intestinal intolerance of carbohydrate. To cite fragments from a paper by Dameshek³⁴ on this subject, "The disease is almost wholly confined to women; the chief complaint is weakness or easy fatigue; other important complaints are belching of gas and a sense of fulness in the epigastrium; diarrhea is occasionally present, but constipation is more likely; a history of a burning or sore tongue is often present; nervousness is almost invariably present; younger women have the atrophied, wrinkled skin seen only in the aged." To this we can add, from our own observations on a small number of patients, the presence of large numbers of Cl. Welchii in the stools. To make this resemblance even closer, Herter³⁵ also commented on premature senility of the skin and muscles and made much of the soreness of the tongue in his cases of intolerance for carbohydrates. We also met with the latter symptom in several of our cases, and in one of these it was the main complaint. In this patient the tongue improved following the strict limitation of carbohydrates in the diet.

Albuminuria was rare in our unselected series but was found in all cases of the toxic group. Remarkable, again, was the disappearance of albumin from the urine of all but one patient following the dietetic regimen. In the single exception albuminuria was diminished but did not disappear altogether. In another case albumin, red blood cells and casts had been observed in the urine for one year, with normal results of tests of renal function. When this patient rigidly restricted the intake of starches, the abnormal constituents of the urine disappeared but reappeared again on several attempts to raise the allowance of starches.

32. Moench, L. M.; Kahn, M. C., and Torrey, J. C.: Analysis of the Fecal Flora in Thirty-Three Cases of Pernicious Anemia, *J. Infect. Dis.* **37**:161, 1925.

33. van der Reis, V.: Die Darmbakterien des Erwachsenen und ihre klinische Bedeutung, *Ergebn. d. inn. Med. u. Kinderh.* **27**:77, 1925.

34. Dameshek, W.: Primary Hypochromic Anemia: II. Clinical Features, *J. A. M. A.* **100**:540 (Feb. 25) 1933.

35. Footnote 7, p. 299. Footnote 2.

Since these patients were not suffering from protein undernutrition, the curative effects of a low carbohydrate diet seem to indicate that the anemia and albuminuria in intestinal intolerance of carbohydrate are in some way associated with the elaboration of toxic substances in the intestine incident to increased fermentation.

Chronic choroidoretinitis was found frequently in our patients, especially among those with other toxic symptoms. It probably is a manifestation of the same intoxication which we suspect of affecting the blood and the kidneys. It is difficult to judge the results of treatment by its effect on choroidoretinitis, because this condition is chronic and in healing leaves scars.

To these signs of systemic intoxication may be added, with certain reservations, extrasystoles, which were also particularly frequent in the group with toxic symptoms. However, the frequency with which extrasystoles and other forms of cardiac consciousness were found, even in patients without toxic symptoms, makes one look for some other explanation. Such an explanation can be seen in excessive abdominal distention, which may embarrass the heart mechanically by pushing the diaphragm up or, as claimed by Fundner,³⁶ may affect the cardiac rhythm reflexly. This, however, does not exclude toxic irritability of the myocardium.

INTESTINAL TOXINS

Substances which may be formed in the intestine that are capable of exerting a harmful local or systemic influence can be divided into two classes: nonspecific toxic substances and bacterial toxins. Among the first are a number of organic acids arising during the fermentation of carbohydrates, which may cause local irritation of sufficient magnitude to produce diarrhea in man.⁹ The most important of these is butyric acid, which is produced in proportions of between 5:1 and 12:1 to the acid next in importance, lactic acid. Weak solutions of butyric acid, when introduced into the colon, produce hyperemia and violent contractions of the colon to a more marked degree than similar solutions of lactic acid.³⁰ Other organic acids formed in the bowel through fermentation are valerianic, propionic, formic and acetic acid, but they are quantitatively unimportant.

Zinsser²⁹ states that the abnormal splitting of carbohydrates may result in stasis of the bowel, with secondary putrefaction and the formation of histamine and other toxic amines. These toxic substances may act locally and, as advocated by Schoen,²⁵ exert a paralyzing action on the smooth muscle of the intestine and blood vessels, thereby inter-

36. Fundner: Ueber den Einfluss intraabdominaler Drucksteigerung und des Füllungszustandes des Magens auf den Blutdruck, *Deutsches med. Wchnschr.* 39: 646, 1913.

fering with the resorption of gases. Or they may become absorbed into the circulation and, if not completely detoxified in the liver, exert a widespread deleterious action. An important objection to such an action of histamine is that, as shown by Mellanby,³⁷ this compound is readily destroyed by bacterial action. In addition, there are reasons to think that histamine is never produced in the presence of carbohydrates.³⁸ In view of this, it is difficult to consider histamine responsible for symptoms in a condition that is particularly aggravated by the intake of carbohydrates which stay longer in the intestine.

Several investigators,³⁹ on the basis of their experiments, came to the conclusion that the intestinal mucosa, at least at some levels, is permeable to bacterial toxins. In addition, Cannon⁴⁰ has shown that the absorption of toxic substances from the intestine is favored by raising the intestinal pressure, and that this is independent of the increase in the mucosal surface. He further states that in gaseous distention both factors may be concerned in the production of toxemias. The bearing of these observations on the conditions existing in our patients is obvious.

Among bacterial toxins, those produced by *Cl. Welchii* have received a great deal of attention. The idea of connecting an overgrowth of this vigorous carbohydrate-fermenting organism with toxic manifestations has its attractions. Through the efforts of a number of workers, notably, Passini,⁴¹ Bull and Pritchett,⁴² Henry,⁴³ Katsumi,⁴⁴ Moench, Kahn and Torrey³² and Kendall and Schmitt,¹⁷ *Cl. welchii* has been shown to elaborate, under certain conditions, several distinct toxic substances: a hematoxin which could account for anemia, a myotoxin which might be responsible for asthenia and extrasystoles, a neurotropic toxin causing symptoms referable to the nervous system and a histamine-like

37. Mellanby, E.: An Experimental Investigation on Diarrhea and Vomiting of Children, *Quart. J. Med.* **9**:165, 1915.

38. Alvarez, W. C.: Autointoxication, *Physiol. Rev.* **4**:352, 1924.

39. Kahn, M. C., and Torrey, J. C.: The Possible Relationship Between Absorption of *B. Welchii* Toxin and Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **24**:413, 1926. Herter.² Moench, Kahn and Torrey.³²

40. Cannon, T. R.: The Effects of Diet on the Intestinal Flora, *J. Infect. Dis.* **29**:369, 1921.

41. Passini, F.: Ueber Giftstoffe in den Kulturen des Gasphlegmonbazillus, *Wien. klin. Wchnschr.* **18**:921, 1905.

42. Bull, C. G., and Pritchett, I. W.: Toxin and Antitoxin of and Protective Inoculation Against *Bacillus Welchii*, *J. Exper. Med.* **26**:119, 1927.

43. Henry, H.: On the Composition of *B. Welchii* Toxin, *J. Path. & Bact.* **26**:497, 1923.

44. Katsumi, Kajima: Beiträge zur Erforschung der Rauschbranderreger: I. Die Toxinbildung des Typus Foth und die toxikologischen, immunisatorischen und biochemischen Eigenschaften des Toxins, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **37**:170, 1923.

substance to which hypotension and other vascular phenomena might be ascribed. Another intriguing aspect of this problem, brought out by Passini,⁴¹ Bull and Pritchett,⁴² Katsumi⁴⁵ and Svartz and Brodd,⁴⁶ is that without sugar in the culture mediums *Cl. Welchii* produces no toxins. It is hard to resist drawing a parallel between these laboratory observations and the presence of toxic symptoms in some cases of intolerance for carbohydrates.

A serious objection to the theory of absorption and systemic influence of toxins from the Welch Bacillus is that it is very sensitive to acid.⁴⁷ Our quantitative bacteriologic studies, which failed to show an overgrowth of *Cl. Welchii* even in some severe cases with toxic symptoms (in the larger series), add a weighty argument against a direct causative relationship between intestinal infestation with this organism and toxic manifestations in our patients. Moreover, the absence of vascular hypotension among patients in the group with toxic symptoms is against Kendall's theory⁸ that a histamine-like toxin produced by the Welch organism is responsible for the hypotension which is frequently seen in this syndrome.

In summing up, we believe that irritating and perhaps toxic products of fermentation materially contribute to the abdominal symptoms of intestinal intolerance of carbohydrate, and that among our patients there is a small but sufficient number who show that it is possible for the intestinal absorption of toxic substances to affect distant organs. As yet there is insufficient evidence to implicate any specific toxic substance or bacterial toxin. During the recent past so many conditions were blamed on "intestinal autointoxication" without convincing proof that a healthy skepticism on this subject is necessary. This, however, should not prejudice one against the possibility of toxic absorption from the bowel, if sufficient evidence in its favor can be presented.

TREATMENT

A therapeutic regimen consisting of three parts has been worked out over several years by one of us (T. L. A.). During the first period a strict limitation of carbohydrates is essential. The patient is permitted to eat with each meal one thin slice of toast or 2 tablespoonfuls of

45. Katsumi, Kajima: Beiträge zur Erforschung der Rauschbranderreger: II. Ueber Toxin und Antitoxin der Typus Foth und Kott und ihre besonderen Verschiedenheiten, Ztschr. f. Immunitätsforsch. u. exper. Therap. **37**:185, 1923.

46. Svartz, N., and Brodd, C. A.: Recherches sur les propriétés hémolytiques du bacille de Welch-Fraenkel obtenu par culture du contenu intestinal, Acta med. Scandinav. **75**:450, 1931.

47. Zeissler, J.: Die Gasödeminfektionen des Menschen, in Kolle, W., and Wassermann, F.: Handbuch der pathogenen Mikroorganismen, Jena, Gustav Fischer, 1928, vol. 4, pt. 2, chap. 14, p. 1099.

macaroni or of a well cooked cereal. The intake of sugar is reduced to a minimum. The following are totally excluded from the diet: potatoes, rice, root vegetables, dried beans, peas, lentils, cabbage, cauliflower, Brussels sprouts, broccoli, peppers, cucumbers, onions, garlic, pickles, spices of all kinds and sweet milk. The patient is allowed ordinary amounts of meat, eggs, fish and cheese, but is advised that the last form of protein is preferable. Green vegetables are to be eaten cooked and puréed. Fruit must be taken either cooked or in the form of juices. There is no restriction of fats. Nuts, except peanuts, are permitted. On such a diet patients miss most keenly the bland carbohydrate articles of food, such as potatoes, bread and rice, which go with the highly flavored proteins. This difficulty is surmounted by advising them to eat every day some cottage cheese and gelatin, which are otherwise used only occasionally. The gelatin can be served with salads or meat and also in the form of desserts.

A special virtue is made of drinking fermented milk. Patients in the clinic are usually given buttermilk, while patients in private practice are asked to take acidophilus milk. Many patients at first develop an exacerbation of symptoms due to fermented milk, so that if the condition is at all marked it is advisable not to prescribe such milk for the first week or two and then to start with small amounts of it, gradually working up to a quart a day.

In addition, colloidal kaolin is prescribed in doses of from 8 to 15 Gm. three or four times a day between meals. Here, again, one must keep within the limits of individual tolerance. The patient must also be advised to keep the bowels open with liquid petrolatum by mouth and, if necessary, by olive oil retention enemas lest hard fecal concretions form from the kaolin. This regimen is to be followed in ordinary cases between two and six weeks.

During the second period carbohydrates, mainly milled starches, sugar and well cooked cereals, are gradually increased in the diet until normal proportions are reached. The administration of fermented milk and kaolin is continued as previously. The approximate duration of this regimen in favorable cases is about one month. Then if the patient is still free from symptoms or nearly so the third part of the treatment can be started.

During the third period an attempt at bacterial implantation is made by putting patients on acidophilus milk or, in case of intolerance, on 4 cc. of a standard culture of *Bacillus acidophilus* three times a day. The patient is also instructed to begin using lactose or lactodextrin at meal time, starting with a teaspoonful and working up to a tablespoonful. At the same time medication with kaolin is discontinued. Such a regimen should be followed for at least two months. After the administration of the *B. acidophilus* preparation is stopped, the patient continues to take lactose with meals indefinitely.

It is again to be emphasized that the administration of fermented milk, of kaolin and of lactose must be adapted to the individual case, and that successive steps in the diet should be prescribed only after the patient has been comfortable on the preceding regimen. We have several times seen enthusiastic interns force on a frail woman with an irritable bowel large amounts of fermented milk, kaolin or lactose, only to have the patient become worse. In the same cases a favorable response was obtained later by proceeding more cautiously.

The purpose of this diet is to limit the total amount of carbohydrates and to confine their absorption as much as possible to the upper part of the small intestine by excluding foods in which the starch is covered by a cellulose membrane. Such a diet decreases fermentation in general and is also directed against the excessive growth of carbohydrate-fermenting, spore-forming anaerobes. The advantage of casein over animal protein is that, according to the work of Cannon,⁴⁰ it encourages an aciduric flora. A number of vegetables which are well known formers of gas and which probably contain irritating substances in addition to starch are excluded from the diet.

Since Graham and Emery⁴⁸ and Hull and Rettger²² showed that dietary changes even with the addition of large amounts of lactose do not influence the acidity of the intestine, fermented milk is given in order to lower the p_H of the intestinal contents by the direct addition of preformed lactic acid. A shift in the reaction of the intestine to the acid side is desirable, as has been stated previously, in order to limit the upward extension of the colonic flora in patients with insufficient gastric acidity. Torrey and Kahn⁴⁹ expressed the belief that an increase in intestinal acidity inhibits particularly the spore-bearing anaerobes, and Kendall, Day and Walker⁵⁰ demonstrated that patients with intolerance of carbohydrate benefit from soured milk, regardless of the organism which ferments the milk.

The efficacy of a commercial preparation of lactic acid in agar in two concentrations was compared in six cases with the action of fermented milk. The results were inconclusive. Since the cost of this preparation is much greater than that of buttermilk, its trial is indicated only in patients who are disinclined to take fermented milk.

48. Graham, W. R., and Emery, E. S.: The Reaction of the Intestinal Contents of Dogs Fed on Different Diets, *J. Lab. & Clin. Med.* **13**:1097, 1928.

49. Torrey, J. C., and Kahn, M. C.: The Inhibition of Putrefactive Spore-Bearing Anaerobes by *Bacterium Acidophilus*, *J. Infect. Dis.* **33**:482, 1923.

50. Kendall, A. I.; Day, A. A., and Walker, A. W.: Chemistry of the Intestinal Flora of Man Containing Abnormal Numbers of Gas Bacilli, *J. Infect. Dis.* **38**:217, 1926.

Kaolin is prescribed for several purposes. As shown by Walker,⁵¹ Dudgeon⁵² and Braadfladt,⁵³ it removes large numbers of bacteria and, according to the belief of these workers, changes the fecal flora, at least in normal persons, to the aciduric type with almost total disappearance of gas bacilli. Furthermore, kaolin is an efficient adsorbent of toxic substances in the intestine. Finally, by coating the intestinal mucosa to which it clings tenaciously, kaolin serves as a barrier against mechanical as well as chemical irritants.

We are particularly interested to know whether the action of kaolin in removing bacteria from the intestine, which was also demonstrated by Braadfladt *in vitro*, is purely mechanical or whether it is a colloidal phenomenon. In the latter event, since practically all bacteria carry negative charges and since kaolin is also negatively charged in neutral and alkaline suspensions, acquiring a positive charge only in acid mediums,⁵⁴ it occurred to us that some substance positively charged in neutral suspension might prove more efficacious than kaolin. This would be of special importance in cases in which insufficiency of hydrochloric acid, by diminishing the acidity of intestinal contents, may interfere with the bacteria-removing action of kaolin. We performed a number of experiments in which the adsorptive ability of various electrically negative and positive substances were tried on suspensions of *Cl. Welchii* and *B. coli* with different p_H values. This work is not completed, but we have had hopeful indications in the use of barium sulphate, calcium carbonate and charcoal, in addition to kaolin.

If the action of kaolin and other compounds in removing bacteria is based on colloidal adsorption, the method of administration of these substances to the best advantage is not indifferent. And since the digestive tract can handle only a certain amount of inert foreign substance, it is particularly important to determine whether repeated moderate doses or a single large daily dose will produce the maximum effect.

Implantation of *B. acidophilus* is attempted because this organism increases the acidity of the intestinal contents by producing lactic acid and also because of its supposed antagonism to the growth of spore-forming anaerobes. Preparations of this organism need to be given only during the third period of treatment, because not until then is the

51. Walker, R. R.: Kaolin in the Treatment of Asiatic Cholera: Its Action and Uses, *Proc. Roy. Soc. Med.* **14**:23, 1921.

52. Dudgeon, L. S.: A Study of the Intestinal Flora Under Normal and Abnormal Conditions, *J. Hyg.* **25**:119, 1926.

53. Braadfladt, L. H.: The Effect of Kaolin on the Intestinal Flora in Normal and Pathological Conditions, *J. Infect. Dis.* **33**:434, 1923.

54. Macleod, J. J. R.: *Physiology and Biochemistry in Modern Medicine*, St. Louis, C. V. Mosby Company, 1930, p. 48.

diet favorable for its growth. To quote from Rettger,⁵⁵ "The ingestion of foreign bacteria alone, even in large numbers does not of itself bring about an elimination or displacement of the common intestinal micro-organisms. Vastly more important is the influence of diet especially milk and lactose." Porter, Morris and Meyer⁵⁶ demonstrated that *B. acidophilus* preparations may aid the establishment of an aciduric flora in children but that this influence is not great.

Simultaneously with the beginning of implantation therapy the patient is given lactose in order to create optimum conditions for *B. acidophilus*. The administration of this sugar must be started cautiously, because patients with this syndrome do not tolerate lactose well and often have a recurrence of their symptoms even with small doses. This was shown in a spectacular manner in two instances in which large amounts of lactose were prescribed by a physician on the strength of a laboratory report of "proteolytic flora." The reaction that followed can aptly be described as an "explosion."

As supplementary therapy, calcium carbonate in doses of 1 teaspoonful is given to patients with much abdominal pain or diarrhea. This drug brings relief, according to Porges and Esser¹⁴ and Bokai,³⁰ by neutralizing butyric acid. We have also indications that, similarly to kaolin, it may remove bacteria from the intestine. The objection to the routine use of calcium carbonate lies in its neutralizing effect on the hydrochloric acid of the stomach, thereby reducing intestinal acidity.

Hydrochloric acid was prescribed for patients with achlorhydria, but it probably cannot be given in sufficient amounts to affect the intestinal acidity.

Diastase, as advocated by Hurst and Knott,⁴ was tried repeatedly in refractory conditions but without success.

Heptyl-resorcinol was given a thorough trial in six patients because of its supposed effect on putrefactive micro-organisms,⁵⁷ but neither the amount of putrefaction nor the formation of gas in beef-heart medium was appreciably changed.

On the suggestion of Dr. G. B. Eusterman and Dr. J. L. Kantor that intolerance for carbohydrate may be a mild form of sprue, liver extract was given to three patients. These patients, who had not improved with other methods of therapy, also failed to respond to liver extract.

55. Rettger, L. F.: The Influence of Milk Feeding on Mortality and Growth, and on the Character of the Intestinal Flora, *J. Exper. Med.* **21**:365, 1915.

56. Porter, L.; Morris, G. B., and Meyer, K. F.: Certain Nutritional Disorders of Children Associated with a Putrefactive Intestinal Flora, *Am. J. Dis. Child.* **18**:254 (Oct.) 1919.

57. Veader, L., and Feirer, W. A.: Di-Hydranol: Control of Intestinal Putrefaction in Man by Oral Administration of 2-4-Dihydroxyphenyl n-Heptane, *Bull. Johns Hopkins Hosp.* **48**:25, 1931.

Our latest venture in the treatment of this condition, directed mainly against flatulence, consists in the administration of vitamin B, on the theory that by increasing the tonus of the intestine we may improve the absorption of gases. In order to avoid simultaneous feeding of carbohydrate we have chosen *vegex* as the most suitable commercial preparation of vitamin B. Our results in a few cases have been encouraging but so far warrant no conclusions.

RESULTS OF TREATMENT

In a little more than one fourth (28 per cent) of fifty consecutive cases marked improvement of gastro-intestinal symptoms was recorded. The patients in this group recovered their ability to eat without trouble ordinary amounts of most carbohydrates with the possible exception of one or two articles of diet. Only two patients maintained that they could take all forms of starch in unlimited quantities and remain free from symptoms. These two, unfortunately, moved without leaving a forwarding address, so that we are unable to substantiate the permanence of their relief.

A little more than one half of the patients (54 per cent) showed partial improvement. In this group are included persons who are reasonably comfortable, but not well, as long as they restrict the amount and kind of carbohydrate foodstuffs in the diet. Most of these patients have periods of better tolerance to starches which, without change in the diet or other apparent reason, are followed by periods of exacerbation of symptoms. Such attacks respond to strict limitation of carbohydrates, and this again seems to increase their tolerance. These obscure fluctuations of tolerance for carbohydrate may be connected with the seasonal occurrence of some intestinal bacteria. Kendall, Day and Walker⁵⁰ claimed to have demonstrated such variations for *Cl. Welchii* in the stools of normal persons, and the same may be true of other micro-organisms.

In addition, some of these patients of their own accord continue to take fermented milk indefinitely, while others cannot get along comfortably without kaolin. On the whole, patients in this group accept with more or less grace permanent dietary restrictions and achieve a higher level of comfort and activity. Perhaps a measure of their improvement is the fear with which most of them contemplate a return to a general diet.

About one fifth (18 per cent) of the patients derived no benefit from any treatment tried. All the patients in this group either had classic mucous colitis, characterized by numerous bowel movements with much mucus after nervous excitement, or passed copious amounts of mucus without outspoken attacks of diarrhea. It was also noticed in general

that treatment was less successful in patients who had noticeable amounts of mucus in the stools and in those who had periodic or chronic looseness of the bowels. The duration of the condition before treatment apparently has no prognostic significance.

No marked shift of the fecal flora to the aciduric type has been observed after the implantation of *B. acidophilus* even in patients who were able to tolerate moderate amounts of lactose (50 Gm. a day) over long periods. In this connection the question arises to what extent it is possible to change the intestinal flora in abnormal cases. Successful experiments of this nature reported in the literature were performed largely on healthy men or animals. In contrast to this is the observation of Torrey¹⁰ on patients with typhoid fever that the degree of transformation of the intestinal flora by diet and lactose depends on the initial type of flora present. He found that when there is a definite putrefactive tendency the change extends only to the elimination of obligate putrefactive organisms and a moderate development of the aciduric types. With a more favorable initial flora he obtained striking changes.

Patients with toxic symptoms were relieved of their gastro-intestinal manifestations so long as they limited the amount of starches in their diet. Moreover, in all the patients with anemia the erythrocytes increased to well within normal limits, and albuminuria disappeared in all but one case. Some of the patients in this group have totally excluded all articles of food rich in starches for periods up to ten years, without any apparent harm.

SUMMARY

A common but not generally appreciated clinical entity, characterized by intolerance of carbohydrate, with complaints centering around marked meteorism, is the subject of the present investigation. Gastro-intestinal and systemic manifestations of this condition were studied in fifty consecutive patients. The more prominent local symptoms are gaseous distention with abdominal pain; excessive flatus; nocturnal colonic distress, and constipation, replaced in severe cases by chronic diarrhea. A background of asthenia, nervousness and vasomotor instability is prominent. In addition, a smaller group of patients had anemia, albuminuria and chronic choroidoretinitis, all probably of toxic origin.

Fermentation tests, quantitative studies of stools for *Cl. Welchii*, aciduric organisms and other features of the intestinal flora permit no consistent correlation with the clinical picture. Extension of the colonic flora into regions of the small intestine where unabsorbed carbohydrates are present and penetration of carbohydrate material into the colon are factors which favor excessive fermentation. Conditions interfering

with the resorption of gases from the intestine, such as loss of tonus by the bowel, also play a large part in the production of flatulence. Irritating organic acids formed during fermentation are probably partly responsible for the local symptoms. The systemic manifestations are probably due to the absorption of some toxic substances the formation of which is favored by the abnormal condition in the bowel.

Strict limitation of carbohydrates, especially starches, in the diet, together with the administration of fermented milk, and kaolin medication afford partial to complete relief in most cases. Coexisting mucous colitis is a complication which seriously interferes with the success of the therapy.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY

STANLEY COBB, M.D.

BOSTON

Since this is the first review of neuropsychiatry to be published in the ARCHIVES OF INTERNAL MEDICINE, with others to follow annually, I shall not confine it to the last year but shall sketch somewhat broadly the ways along which advances have been made in the last several years. Physiologic and psychologic discoveries are considered important enough to be discussed here because they are either precursors of therapy or elucidators of empirical treatment. Successful new methods of treatment are few but will be emphasized because of their practical use to the physician. In a brief paper only a few topics can be discussed. For those who wish to read more extensively, two books in English are recommended: "The Problem of Mental Disorder," a collection of twenty-five current points of view, edited by Madison Bentley,¹ and "Recent Advances in Neurology" by Brain and Strauss.² In German the monthly review journal *Fortschritte der Neurologie, Psychiatrie und ihrer Grenzgebiete* is most helpful.

THE PSYCHOGENIC ORIGIN OF SOMATIC LESIONS

Improvement in the cooperation between internist and psychiatrist has been conspicuous recently because of the better understanding of psychosomatic interrelationships. The paper by Moschcowitz³ is an excellent example. He gave instances of the definite causal relation between reiterated emotional reactions and well established anatomic lesions in such diseases as exophthalmic goiter, essential hypertension, gastric ulcer and mucous colitis. That emotion may cause profound functional changes is acknowledged. Moschcowitz expressed the belief that prolonged abnormal function may result in profound anatomic change. Hitherto, pathologists have not recognized that such a sequence exists, because of the domination of the belief that morbid anatomy comes first and abnormal function follows. Among physiologists, Cannon⁴

1. Bentley, M., and Cowdry, E. V.: *The Problem of Mental Disorder*, New York, McGraw-Hill Book Company, 1934.

2. Brain, W. R., and Strauss, E. B.: *Recent Advances in Neurology*, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1934.

3. Moschcowitz, E.: *New England J. Med.* **212**:603, 1935.

4. Cannon, W. B.: *Bodily Changes in Pain, Hunger, Fear, and Rage*, ed. 3, New York, D. Appleton & Company, 1929.

has led the way and given experimental proof that emotions change bodily functions.

The Josiah Macy Jr. Foundation is to be congratulated on having aided H. F. Dunbar⁵ in compiling an extensive survey of the literature on emotions and bodily changes. In a general way most physicians believe that the mind affects the body, but actual data have not been easily available. This book gives literally hundreds of specific instances from the fields of endocrinology, metabolism, cardiology, gastroenterology, dermatology and the like. For example, well authenticated cases are given of hair turning white or falling out after a severe fright. Three different experimenters have produced blisters on the skin by hypnotic suggestion; thus it is easier to accept the excellent clinical evidence for the occurrence of spontaneous hysterical ecchymoses. Cases are cited in which fever of psychogenic origin has been carefully observed and then cured and reinduced by hypnotic suggestion. The gastro-intestinal disorders produced by emotional stress are remarkably common and varied—all the way from the psychic influence on salivary secretion, which is common knowledge, to the psychogenic hypermotility and hypersecretion which lead to peptic ulcer. The evidence for this last stage, the development of the ulcer, is less direct, but the number of observations is impressive. One could go on and on quoting anecdotes from this book; the lesson to be learned, therefore, is that these occurrences are not extraordinary but can be seen at all times by the physician.

The use of the word "functional" to denote "psychogenic" or "emotional" is to be deplored. Even in Dunbar's book it is misused. Jelliffe⁶ put the case well by saying: "I talk of 'reversible and irreversible' organic changes, never of 'organic' changes. Organic changes are always taking place in all functioning organs. Any one should know that; whether within the physiological range and whether reversible or not is the important consideration." Two writers in Bentley's⁷ book "The Problem of Mental Disorder" have stressed the importance of the definition of such terms. Under the heading of "A Dichotomy in Psychiatry and Medicine: 'Organic' and 'Functional' " ⁷ one reads: "I do not know of any function without structure . . . if we mean by the term 'functional disease' that etiology and pathology are unknown, it would

5. Dunbar, H. F.: *Emotions and Bodily Changes*, New York, Columbia University Press, 1935.

6. Jelliffe, S. E.: *Arch. Neurol. & Psychiat.* **30**:239 (July) 1933, in reply to a book review on his *Psychopathology of Forced Movements and the Oculogyric Crises of Lethargic Encephalitis*, Washington, D. C., Nervous and Mental Disease Publishing Company, 1932.

7. Bentley and Cowdry,¹ p. 34.

be better to say so. The medical psychiatrist . . . *has no use for the metaphysics which separate mind and body.*" Later in the book⁸ it is stated:

The great stumbling block to effective cooperation between physician and psychiatrist is the widely and complacently accepted idea that all diseases can be divided into two categories, and classified as either "functional" or "organic." It is extraordinarily difficult to explain to a man trained in the school of pathological anatomy that his criterion for calling one disease organic and another functional is entirely artificial, that the deciding factor is the instrument he happens to use to record the abnormality of the organ under observation. Just at present the instrument most relied upon is a microscope with a limit of magnification of about twelve hundred diameters. Suppose that some physicist tomorrow invents a microscope with a much greater useful magnification. At once abnormality may be seen where none was previously visible. But why confine ourselves to the microscope? Certainly there are other ways of recording abnormality of the human organism besides visual observation of fixed and sectioned tissue. For example, the spectroscope may show that a certain type of sugar is found in the urine of an athlete before a contest. This is an observation which may be recorded photographically; it is a phenomenon which can be shown to occur regularly; by chemical methods the sugar may be estimated quantitatively. The average histopathologist, nevertheless, will strenuously maintain that there is no organic pathology in this anxious athlete, and that the disease is "merely functional." What the histopathologist really means is that after an autopsy on this athlete no lesion would be visible in stained sections of tissue, with a microscope of the type used in the year 1934.

To attack the subject from another angle one has only to consider the numerous diseases where chronic functional disturbance leads to organic lesion. It is known that sudden fright may precipitate Graves' disease, with exophthalmia, enlarged thyroid gland, and increased metabolic rate. A somewhat more complicated situation was presented to me by a patient who came to the clinic with the mental, neurological, and dermatological symptoms of pellagra. At autopsy, the nerves, cord, and brain showed typical neuronal lesions. Yet primarily, as the history showed, the patient's trouble was fear. This had early made him a recluse, later led to restriction of diet and eventually to pellagra. In this case there was certainly gross and microscopic organic pathology. But who can draw a line showing where "mental" cause ceased and "physical" cause began?

It may seem pedantic to expatiate upon the impossibility of drawing a line between "organic" and "functional," but experience shows that it is necessary to emphasize that no such line can logically be drawn. If it is drawn arbitrarily, its position is ordained by the point to which technology has advanced in that year. It depends on what kind of a "scope," "graph," or "meter" is used by the observer. In other words, the line between organic and functional (and between physical and mental) is an artefact. . . . Structure and function are inseparable.

THE HUMORAL TRANSMISSION OF NERVOUS IMPULSES

The discovery of humoral agents in the transmission of nervous activity from nerve to muscle is a physiologic advance which probably has momentous implications for neuropsychiatry. Loewi was the first

8. Bentley and Cowdry,¹ p. 111.

to demonstrate clearly the chemical transmission of nervous effects by showing that the effect of vagal stimulation on a frog's heart is due to an agent which is formed in the muscle and then circulates in the blood. Sir Henry Dale⁹ has almost certainly identified this substance as acetylcholine. Another substance which transmits effects like those caused by stimulation of the sympathetic system has been found by Cannon.¹⁰ This has been named sympathin and has properties that suggest a close relationship to epinephrine. It is clear that the heart is controlled by the opposing effects of these two chemical substances liberated among the fibers of the cardiac muscle. Furthermore, recent work from Dale's laboratory indicates that every ordinary motor nerve impulse to a fiber of a voluntary muscle produces a tiny charge of acetylcholine in contact with the receptive plate of the muscle fiber. In his address at the opening of the Lilly Research Laboratories in October 1934 Dale said:

For the whole of the peripheral nervous system, then, we seem to be in sight of knowledge enabling us to describe the transmission of effects, from nerve fibers to receptive cells, in terms of precise chemistry. And the vast and complex problem of the central nervous system still remains. It will be strange, indeed, if knowledge of this kind, expanding just now with such unexpected rapidity, does not eventually have some effect, if only an indirect one, on practical therapeutics.

Optimistic though this may seem and possibly open to the criticism that the evidence is incomplete and not corroborated by other workers, the discoveries are certainly important for those interested in nervous and mental disease.

Some corroboration comes from the zoologic researches of Parker.¹¹ He observed in certain fishes two classes of nerve fibers to the chromatophores, one expanding the chromatophore and the other contracting it. These apparently act by secreting neurohumors at the nerve terminals. If the blood from a flat fish, dark in consequence of a long sojourn on a dark background, is withdrawn and injected into a light fish, a dark spot due to the expansion of the chromatophores appears near the site of the injection; vice versa, a light spot may be produced on a dark fish.

MYOPATHY

In the field of muscular dystrophy and atrophy some order seems to be emerging from the chaos of syndromes. There appear to be three groups¹² of primary atrophies. The first is made up of sporadic

9. Dale, H. H.: *Science* **80**:343, 1934.

10. Newton, H. F.; Zwemer, R. L., and Cannon, W. B.: *Am. J. Physiol.* **96**: 377, 1931. Cannon, W. B., and Bacq, Z. M.: *ibid.*, p. 392.

11. Parker, G. H.: *Humoral Agents in Nervous Activity*, New York, The Macmillan Company, 1932.

12. Aring, C. D., and Cobb, S.: *Medicine* **14**:77, 1935.

diseases: amyotonia congenita, progressive muscular atrophy and amyotrophic lateral sclerosis. These are not familial. The second is the group of hereditary myopathies in which lesions are almost entirely in the muscles but associated with a significant amount of abnormality in the endocrine glands. In this group creatine metabolism is most abnormal.¹³ The third is a group of strongly inherited diseases due to pathologic conditions in certain tracts of the spinal cord. These are true system diseases and are related to many nervous disorders which are not commonly associated with muscular atrophy or dystrophy. It is only in the second group of diseases that progress is being made in treatment. Here the therapeutic use of amino-acetic acid¹⁴ seems to result in improvement in some patients. The supposition is that in this group of myopathies the body has lost its ability to utilize creatinine. Ephedrine has been found beneficial, especially for myasthenia gravis,¹⁵ and it also has been used as an adjunct to treatment with amino-acetic acid. Most helpful of all, however, is the recent use of the di-methylcarbamic ester of m-oxyphenyl tri-methyl ammonium methylsulfate¹⁶ for myasthenia gravis. It gives immediate and striking relief, but the effect apparently lasts for only a short time. Experimental investigations suggest that myasthenia is due to a delayed restoration of normal chemical relations at the myoneural junctions after fatigue. This delay interferes with the passage of excitation from a motor nerve to the end-plate of a muscle. It is possible that drugs of the physostigmine group act on acetylcholine at the end-plate.¹⁷

ELECTRO-ENCEPHALOGRAPHY

The technic of neurophysiology has been so much improved lately by the advances in physics that now, by the use of the radio amplifier and the oscillograph, the investigator of electrophysiology can record changes in electrical potentials of the intensity of a thousandth of a volt and of a duration of a ten thousandth of a second. These are recorded photographically. Such an armamentarium makes possible the recording of minute changes in potential (action currents) in the brain, even through the skull. Records of these changes are called electro-encephalograms, and they show as wavelike variations in the voltage; hence the popular name "brain waves." Experiments have shown that there is almost constant cerebral activity, greater in the association areas of the cortex than in the projection areas. Special regions of the cortex, such as the visual area in the occipital lobe, can be made

13. Milhorat and Wolff: *Internat. Neurol. Cong.*, 1935, abstr. vol., p. 55.

14. Milhorat, A. T.: *Deutsches Arch. f. klin. Med.* **174**:487, 1933.

15. Edgeworth, H.: *The Effect of Ephedrine in the Treatment of Myasthenia Gravis: Second Report*, *J. A. M. A.* **100**:1401 (May 6) 1933.

16. Pritchard, E. A. B.: *Lancet* **1**:432, 1935.

17. Pritchard, E., and Blake: *Internat. Neurol. Cong.*, 1935, abstr. vol., p. 103.

to produce complex waves by stimulation of the optic nerve.¹⁸ The administration of drugs and the induction of anesthesia modify these responses. During sleep¹⁹ much activity goes on. In the early part of a period of sleep there are series of waves which are fairly regular and gradually become lower in amplitude and more random in type. When the subject is aroused the waves immediately become more numerous, regular and larger. This change seems to be in relation to the changes in the level of consciousness. In epileptic patients²⁰ special forms of waves have been observed preceding attacks of both petit mal and grand mal. Most interesting are smaller waves of a similar form which sometimes occur in these patients without being followed by a clinical seizure, as if a subliminal fit were being recorded. The diagnostic possibilities suggested by this work are great.²¹ The limitation of the method seems to be the complexity of the brain itself; too many and too complex processes are going on at once. Studies of seizures, of states of consciousness and of special senses are obviously important, but it seems improbable that correlations with complex "mental" changes or psychologic variations can ever be made by this method.

EPILEPSY

Marked progress has been made in the understanding of epilepsy. At the International Neurological Congress in London in July 1935 a whole session was given over to this subject, and the many papers presented accurately reflect a new point of view. Abadie (Bordeaux) stated clearly that the time is past when epilepsy can be considered to be a disease; it is a syndrome or manifestation of a lesion of the central nervous system. The old doctrine of idiopathic epilepsy has been entirely abandoned. Abadie even said that epilepsy is always an acquired disorder, never inherited. With that statement many would not agree, for although inherited epilepsy is much less common than most textbooks would lead one to believe, convincing evidence is available that it may be inherited either alone²² or with migraine.²³ A fine paper by Lennox (Boston) summed up the physiologic pathogenesis so well that the abstract is largely quoted:

In patients having frequent seizures, certain alterations of physiological processes in the brain (water balance, acid-base balance, oxygen or blood supply)

18. Bishop, C. H., in Bentley and Cowdry.¹

19. Loomis, A. L.: *Science* 82:198, 1935.

20. Gibbs, F. A.; Davis, H., and Lennox, W. G.: *Studies in Epilepsy: Alterations in the Electro-Encephalogram Occurring in Epilepsy and in Other Conditions Characterized by Loss of Consciousness*, *Arch. Neurol. & Psychiat.* 34:1133 (Dec.) 1935.

21. Kornmuller, A. E.: *Fortschr. d. Neurol., Psychiat.* 7:391, 1935.

22. Goldstein, M.: *Internat. Neurol. Cong.*, 1935, abstr. vol., p. 34.

23. Ely, F. A.: *The Migraine-Epilepsy Syndrome: A Statistical Study of Heredity*, *Arch. Neurol. & Psychiat.* 24:943 (Nov.) 1930.

modify the frequency of seizures. Alkalosis induced by overventilation or by ingestion of alkali tends to increase seizures; acidosis induced by fasting, by a ketogenic diet, by ingestion of acids or acid-forming salts, by breathing carbon dioxide or by muscular activity tends to decrease seizures. The total blood flow through the brain, as measured by a thermo-electric blood-flow recorder inserted in the internal jugular vein, does not show reduction immediately before the seizure except when the seizure is induced by overventilation. These observations prove that generalized cerebral anemia is not the cause of spontaneous seizures. The total oxygen consumption and oxygen content of the blood are normal.

An acute cerebral anoxemia was produced in two ways: By breathing of pure nitrogen and by induction of orthostatic syncope consequent on ingestion of sodium nitrate. Results differed in patients having grand mal and those having petit mal seizures. Out of twenty grand mal cases rendered unconscious by one of these procedures, only one experienced his usual type of grand mal seizure. In thirteen patients having frequent petit mal, with or without mild localized convulsive movements, the patient's usual seizure was readily and consistently induced by an induction of anoxemia or cerebral anemia. Usually the degree of anoxemia was insufficient to produce unconsciousness in the normal individual.

The electro-encephalogram shows that petit mal seizures are invariably preceded or accompanied by a burst of electrical potentials about ten times the voltage and about one fifth the frequency of the patient's usual potentials. When clonic movements are present, they are synchronous with these large waves; similar voluntary movements are unattended by differences in electrical potentials. The form of the large waves is individual for each patient. Furthermore, the electro-encephalograms of patients, taken between attacks, show small disturbances of rhythm suggestive of larval or sub-threshold seizures. Induction of alkalosis by hyperpnoea, of anoxemia by nitrogen breathing and of cerebral anemia by fainting (in both patients and normal persons) also causes waves of increased magnitude and decreased frequency. With increasing alkalosis or anoxemia, these currents become larger and larger until the patient's typical form of action currents (and the accompanying seizure) appears.

At the International Neurological Congress Minkowski (Zurich) described the pathology of the brain in persons subject to seizures. He said that some pathologic change is always observed if the histologic work is careful and thorough enough. Ulrich (Zurich) described a successful method of bromide therapy in which the dosage was controlled by careful quantitative estimations of the amount of bromide in the blood. Penfield (Montreal) spoke on surgical therapy. He pointed out that a focal lesion of the brain is often present even in cases of "idiopathic" epilepsy. When the history, the presence of neurologic signs or the pattern of the attacks suggests the possibility of a focal lesion an encephalogram should be made. Also, an attack should be observed even if it has to be induced. At operation the cortex should be investigated by electrical stimulation. The lesions which lend themselves to surgical treatment are scars uniting the meninges to the brain and areas of cerebral atrophy. Penfield said that of twenty-two patients treated by radical excision of a meningocerebral cicatrix, ten had remained free from attacks and seven were much improved. In

twenty-two additional cases radical excision of areas of focal atrophy and focal cerebral cicatrix had been performed; nine of these patients were free from attacks, and seven were improved.

The treatment of epilepsy by means of hypodermic injections of acetylcholine has been tried by several investigators with apparently beneficial results.²⁴ The theory is that since cerebral vascular spasm may start the attacks, a vasodilator substance may prevent them. The mistake in all such arguments lies in the fact that epilepsy has no one cause; it is a symptom that may be produced by any one of fifty or more pathologic conditions. Some fits doubtless are due to spasm of cerebral arteries, but before therapy is instituted the pathogenesis of the seizure in each case should be carefully studied, and treatment appropriate to that particular case should be given. Generalizations about epilepsy are useless.

MIGRAINE

Much investigation into the cause of migrainous headache has been carried on during the last three years. The excellent review by Riley²⁵ in 1932 summed up the knowledge to that date. There has been a sad lack of autopsy material. Physiologic researches have fared better, and it has been shown that the walls of the meningeal vessels are sensitive and that changes in pressure which distort these walls cause headache.²⁶ Furthermore, ergotamine tartrate has been found to be effective in relieving and aborting attacks of migraine²⁷ in from 40 to 90 per cent of cases.²⁸

TREATMENT OF DEMENTIA PARALYTICA

Experience is fast accumulating that proves the worth of the fever treatment of neurosyphilis. With careful handling a good remission with return to work is to be expected in 40 per cent of patients with an early stage of the disease, and an additional 20 per cent show distinct improvement. Infection with malaria is still the method most used, but typhoid vaccine is effective and advisable for patients not physically fit to withstand malarial infection.²⁹ A marked increase in the occurrence of hallucinations has been reported by several authors during fever therapy.³⁰ Hyperpyrexia induced by other methods is becoming

24. Stander, K. H.: *Fortschr. d. Neurol. & Psychiat.* **6**:419, 1934.

25. Riley, H. A.: *Bull. Neurol. Inst. New York* **2**:429, 1932.

26. Clark, Hough and Wolff: *Internat. Neurol. Cong.*, 1935, abstr. vol., p. 47.

27. Lennox, W. G.: *New England J. Med.* **210**:1061, 1934.

28. Kennedy, F.: *Bull. New York Acad. Med.* **11**:511, 1935.

29. Schnitker, M. T.: *Treatment of Dementia Paralytica with Typhoid H Antigen Vaccine: Report of Twenty-Five Cases in Which Fever Therapy Combined with the Administration of Tryparsamide Was Used*, *Arch. Neurol. & Psychiat.* **31**:579 (March) 1934.

30. Pap, Z.: *Arch. f. Psychiat.* **102**:57, 1934.

more effective. Diathermy³¹ has given improvement in as many as 50 per cent of cases, but the danger of burns is ever present. Hot baths have been used but are too exhausting to the patient. Hot-air cabinets are effective. Perhaps the safest and simplest device is the electric blanket,³² which is easily controlled and keeps the patient's temperature at from 104 to 105 F. by mouth for several hours without discomfort.

Various methods of radically changing the level of consciousness of a psychotic patient have been used in the treatment of mania, depression and catatonic stupor. A mixture of the di-ethylamine salts of di-ethylbarbituric acid and allylisopropylbarbituric acid,³³ paraldehyde, amylene hydrate, chloral³⁴ and other drugs have been used. The patient is kept in a prolonged narcotic state, sometimes for two weeks. The amount of improvement obtained is not impressive. Amytal also has been used to remove inhibition and cause the patient to talk about his repressed fears during the excited stage preceding sleep or during the period of awakening. It seems to have been an aid in hastening psychotherapy in many cases. The use of inhalations of carbon dioxide and oxygen to arouse a patient from stupor has had dramatic results, but although the improvement is remarkable, it appears to be short lived. As a result of this experience prolonged sojourn in an oxygen chamber has been tried on the basis of the theory that there is a state of cerebral suboxidation in dementia praecox. So far the results have been disappointing.

MULTIPLE SCLEROSIS

As long as the pathogenesis of multiple sclerosis remains unknown, no good results of treatment can be expected. The spirochetal and virus theories of etiology have been discredited. Various other explanations of the disease are being brought up; exacerbations of the symptoms have been found to be related to barometric changes,³⁵ and in fifty-nine of eighty-nine patients with multiple sclerosis a myelolytic agent has been isolated from the urine.³⁶ The theory that seems to fit most clinical and pathologic facts is the one proposed by Putnam³⁷ on the basis of several years' experimental work. He expressed the belief that

31. Graham, N. B.: *Brit. J. Phys. Med.* **8**:157, 1934.

32. Epstein, S. H.: *New England J. Med.* **212**:611, 1935.

33. Ström-Olsen, R., and McCowan, M. L. M.: *J. Ment. Sc.* **80**:658, 1934.

34. Cloetta, M., and Maier, H. W.: *Ztschr. f. d. ges. Neurol. u. Psychiat.* **150**:146, 1934.

35. Petersen, W. F., and Milliken, M. E.: *Mental and Nervous Diseases, in The Patient and the Weather*, Ann Arbor, Mich., Edwards Brothers, Inc., 1934, vol. 3.

36. Weil, A.: *Internat. Neurol. Cong.*, 1935, abstr. vol., p. 53.

37. Putnam, T. J.: *Studies in Multiple Sclerosis: IV. "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction*, *Arch. Neurol. & Psychiat.* **33**:929 (May) 1935; *Internat. Neurol. Cong.*, 1935, abstr. vol., p. 51.

multiple sclerosis and certain forms of acute disseminated encephalomyelitis represent different stages and degrees of the same process. Both conditions have been stimulated in animals by the use of minute doses of tetanus toxin; a series of lesions resembling encephalitis in acute stages and sclerotic plaques when chronic have been produced in animals by the obstruction of cerebral venules. These results agree with the histologic observation of thrombi in the venules of human beings. Moreover, Putnam has observed a peculiar lability of the coagulation of the blood in patients. Thus it seems that one of a number of infectious or exogenous factors may activate the clotting mechanism to an abnormal degree, with the resulting formation of thrombi in the venules and of plaques of demyelination about them. Such an explanation at present gives no specific indication as to therapy. It strengthens the conservative belief, however, that rest in bed during an exacerbation and an open-air regimen with much rest and sunshine between attacks, combined with a careful search for and removal of foci of infection, comprise the best treatment at present.

PSYCHONEUROSIS

In the history of medical research one finds over and over again that progress in the knowledge of the pathogenesis of a disease and in the treatment of a disease is made only after the disease can be reproduced in laboratory animals. It is therefore encouraging to learn that Pavlov has been able to reproduce in dogs psychologic conflicts which make them behave rather like persons suffering from minor psychoses ("neuroses"). He was able repeatedly to cause a state of "pathologic inertness," which he thought resembled human obsessional neurosis. The production of abnormal mental states in dogs is an important advance, but his speculative discussion of the type of psychopathology and the comparison with syndromes in human beings seem to me far-fetched. Corroboration of Pavlov's experiments is already available from Liddell's³⁸ laboratory at Ithaca, where for eight years sheep have been observed with an "enduring derangement of behavior" resulting from "a conditioning routine" to which they could not adequately adjust themselves. Bromide and endocrine therapy have been tried on these "neurotic" animals with beneficial results.

Psychoanalysis continues to be used more and more for the treatment of the minor psychoses. Even the opponents of the freudian school admit that the method has one great advantage: the analyst starts by explaining to the patient that treatment will take at least a year and that success will depend on the patient's work, not that of the analyst. Thus the long and arduous task of reintegrating a per-

38. Liddell, H. S.; Anderson, O. D.; Kotyuka, E., and Hartman, F. A.: *Am. J. Physiol.* **113**:87, 1935.

sonality is begun with the shoe on the right foot. With too many of the shorter methods the patient starts out optimistically but is disappointed after a few months. The latest book by Freud,³⁹ entitled "New Introductory Lectures on Psychoanalysis," is a continuation and elaboration of his twenty-eight lectures published in 1917. There is a good chapter on education, in which he says that in a short span of time the child has to attain instinctual control and social adaptation and that much of this must be forced on him. The function of education is "to inhibit, forbid and suppress." One must steer between "the Scylla of giving the instincts free play and the Charybdis of frustrating them." The chapter entitled "Revision of the Theory of Dreams" impresses me as being a valuable contribution; certainly in this field the author has given to psychology and psychiatry a new way of understanding primitive thinking—"grammarless speech" and "the raw material of thought." The dogmatic interpretation of symbols, however, and the insistence on the thesis that "all dreams are wish fulfillments" are not easily accepted. There are too many positive statements; words like "absolutely certain," "inevitable" and "always" appear too often. In a discussion of the reaction of such a highly organized biologic unit as man such dogmatic statements are simply inaccurate. The book is written with artistry, and many passages show such keen insight and almost inspired intuition that they take hold of the rapid reader and convert him to the author's point of view. Careful reading, however, leaves the impression that Freud is a great man, certainly, an artist and a philosopher with an extraordinary intuitive faculty. He has probably made some remarkably shrewd guesses, which cannot be proved or disproved for many years to come. He weaves theories on weak evidence and elucidates aspects of human behavior that have heretofore been inexplicable. He sees deep into human nature. All great authors have done this, and some philosophers, but it is not science.

39. Freud, S.: *New Introductory Lectures on Psycho-Analysis*, translated by W. J. H. Spott, New York, W. W. Norton & Company, Inc., 1933.

Book Reviews

Blood Groups and Blood Transfusions. By Alexander S. Wiener, A.B., M.D., Brooklyn. Price, \$4. Pp. 220, with 41 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

This book brings together in a readable form practically everything that is known today about blood groups and the bearing that the subject has on the general biologic problem of the individuality of blood of different persons and animals. Although knowledge about such matters is but thirty years old and Wiener has by no means attempted to include all the references to literature, he has referred to considerably more than five hundred articles, monographs and books.

The author deals with the technic of detecting the four major groups, O, A, B and AB, some rather definite subgroups and the agglutinogens M and N, giving a preference, when routine groupings are done, to the Landsteiner method when a large number of serums are to be examined and to the slide method for testing one or two specimens. The various properties of the four groups are discussed, and the sources of error in grouping are clearly set forth. There follows a section dealing with the history of blood transfusion, the selection of donors and indications for and reactions to transfusions. Outside of definite incompatibilities, gross errors and accidents, no definite information is presented to explain the low grade post-transfusional reactions seen by all those who do many transfusions. The author, apparently leans toward the citrate method but gives a discussion of all the methods in common use, pointing out the fact that the citrate method does not, in the hands of those experienced, produce more reactions than the direct methods. He could have expanded his criticism of certain apparatus for direct transfusions that are on the market, in particular, their failure to protect the donor adequately.

The most important sections deal with the inheritance of blood groups and other peculiarities of blood. The discussion is elaborate and mathematical. Bernstein's theory of three allelomorphic genes, A, B and R, is supported, and the evidence on which this argument is based is presented.

The anthropologic investigations are of considerable interest, and tables containing valuable information are numerous. It is noted that factor A, although decreasing from the West to the East, never becomes rare, whereas factor B becomes rare among western people. Theories for this are offered. Other chapters deal with groups in animal blood and the relation of the distribution of groups to clinical diagnoses, a field which has been, for the most part, nonproductive.

The final chapter deals with the medicolegal aspect of the subject, clearly setting down the backwardness of American courts in accepting such scientific evidence and the obvious usefulness of blood groups in settling many matters of dispute involving parentage and other matters. As yet, no record in a judicial decree in which grouping has been mentioned as the basis of the court's decision is available. A final warning is sounded that one who would appear in a court as an expert in such a case should be not only competent but well fortified by carefully performed tests and should have a vast experience in the study of biologic differences in human beings.

As a whole, the book is practical and clear, with enough detail to save the reader much time in looking up original material.

Radiologie clinique du tube digestif: I. Estomac-duodénum. By Pierre Duval, J. Ch. Roux and Henri Bécère. Part 1: Estomac. Part 2: Duodénum. Second edition. Cloth. Price, 330 francs. Pp., part 1, 252; part 2, 122, with 514 illustrations and 516 drawings. Paris: Masson & Cie, 1935.

The first edition of this work appeared seven years ago and was exhausted in about eighteen months. This, the second edition, was inspired by the advances

that have taken place in the roentgenology of the alimentary canal, especially those resulting from more punctilious demonstration of the mucosal relief, and the internal topography is given particular attention throughout. Although the work is essentially an atlas with profuse and excellent illustrations, the text is nevertheless amply explanatory, and the employment of drawings to elucidate the roentgenograms adds to its instructiveness.

After presenting the normal stomach with its variants, anomalies, functional alterations and displacements by extrinsic cancer, the intrinsic diseases of the viscus are discussed individually and, for the most part, thoroughly. The normal duodenum and the duodenum with a pathologic condition are handled similarly.

Although in the main the work follows conventional lines, a few surprises await the reader. Of gastritis, for example, the authors state that it is impossible at this time to describe the roentgen expression of this disease and that previous descriptions have been given without histologic controls. Continuing, the authors point out that the normal gastric mucosa is constantly mobile, with multiple and infinitely variable aspects, that Montier has never been able to establish any correspondence between the roentgen and gastroscopic appearances of the rugae in gastritis and that from histologic studies the authors have found that the roentgen images of healthy and profoundly affected mucosa are indistinguishable. Likewise, the authors hold that gastric syphilis has no pathognomonic roentgen signs and that the examination is incapable of contributing any information whatever to the etiologic diagnosis. And this from France whose syphilologists excel those of the world!

Other notable features of these volumes are the excellent chapter on the stomach after operation; absence of any reference to duodenitis, although periduodenitis is discussed at length, and the demonstration and differential criteria of the ampulla of Vater.

In the prospectus it is stated that the pupils of Professor Duval and the editors will be proud if foreign readers will say of this work that by its method and clarity of exposition the book is "very French." Their pride is warranted, but if any one conjectures that the work is prolix or imaginative he will be surprised to find that it is terse and extremely conservative. Any American radiologist who can read French at all will be able to understand the text and will derive pleasure and profit from the possession of this new contribution.

Klinik und Therapie der Herzkrankheiten. By Dr. D. Scherf, Assistant in First Medical University Clinic, Vienna. Price, 6.60 marks. Pp. 210, with 10 illustrations. Berlin: Julius Springer, 1935.

This is a delightfully practical booklet summarizing for practicing physicians the essential features of the short course in cardiology given each year in the First Medical University Clinic at Vienna. This course, one gathers, is very brief and solely for the benefit of physicians in general practice who wish to brush up on new methods of treating the common cardiac disorders that are seen most frequently.

Scherf states in his preface that there is no lack of good textbooks on heart disease to which any one can refer. His aim is not to attempt a new textbook but instead to set down as best he can the essentials of recent progress in cardiology and, especially, of progress in the art of making persons with heart disease as comfortable as possible.

He has little to say of electrocardiography and the roentgen rays, of congenital heart disease or of acute or subacute bacterial endocarditis. On the other hand, he has a great deal to say regarding the clinical picture of chronic cardiac decompensation: breathlessness, paroxysmal dyspnea of various types, chronic passive congestion and edema.

He is interested in describing the physical signs of the various valvular lesions and how accurate a diagnostician an intelligent observer can become if he is willing to train his eyes, hands and ears. He also lays proper emphasis on angina pectoris and disorders of the heart muscle.

About a quarter of the volume is devoted to therapy, for instance, to the proper and varied use of digitalis or its derivatives and morphine, with comments on the diuretics, the therapeutic use of bleeding and the intravenous injection of hypertonic dextrose solution. There is an excellent section on the management of cardiovascular syphilis, with due warning against the overenthusiastic use of arsenic without proper preliminary preparation, and another on the question of the proper type of diet for patients with heart disease.

At the end of the book is a comprehensive table of contents with page references so that one can quickly look up anything covered in the subject matter. There are practically no references to the literature, for the book is written as though the author were talking to his students, giving them the benefit of his own ideas and experience. On the whole, the monograph is a highly personal one, excellently written, and should prove a great boon to those for whom it was intended.

The Relation Between the Vitamin B Requirements and the Relative Quantity of Proteins, Fats and Carbohydrates in the Diet. (In Danish, with a summary in English.) By Dr. P. Vogt-Møller. Pp. 165. Copenhagen: Levin & Munksgaard, 1934.

This monograph is a detailed account of a well controlled and extensive experiment (on mice) to determine whether the optimum requirements of the different vitamin B factors (B_1 , B_2 , B_4) vary with the relative quantity of three energy foods (proteins, fats, carbohydrates) in the diet. The criteria used were: growth, longevity and specific symptoms of avitaminosis. In the basal or standard diet protein (purified casein) made up 31 per cent; purified rice starch, 38 per cent, and Crisco, 22 per cent. To these were added: cod liver oil, 2 per cent of the diet; a mixture of sodium chloride, 7 per cent, and 1 drop of wheat germ oil daily.

In the high fat diet Crisco replaced starch entirely and made up 50 per cent of the diet, and the protein was raised to 39 per cent. In the high carbohydrate diet fat was eliminated, the rice starch raised to 70 per cent and the casein reduced to 25 per cent. Two diets high in protein were used. In one the 69 per cent casein was supplemented by 22 per cent Crisco; in the other 84 per cent casein was supplemented with 11 per cent rice starch. The calories per gram of diet remained essentially the same.

The results show that in mice, with the type of diets used, the minimum and optimum requirements of vitamin B_1 and B_4 increase with the increase in the carbohydrate fraction in the diet. The same relation obtains between vitamin B_2 and the fat in the diet. The results with diets high in protein were less conclusive, but indicated that the higher the protein content the greater the amount of vitamin B_2 necessary to prevent the development of pellagra. It is of interest to note that these and other studies have verified, in part, the original theory of Dr. Ejkmán, that beriberi is due to chronic excess of starch in the diet.

Illustrative Electrocardiography. By Joseph H. Bainton and Julius Burstein. Price, \$5. Pp. 258, with 100 plates. New York: D. Appleton-Century Company, Inc., 1935.

This is really an atlas of electrocardiography illustrating a great variety of normal and abnormal tracings with brief explanatory notes. Within the limits of such a project the execution is excellent; one wonders, however, whether any real purpose is served, since the expert is familiar with all this material, and the physician who is inexperienced can hardly train himself by the atlas method. However, for the physician who wishes to have at hand good illustrative curves of the various disorders of the cardiac mechanism for ready reference the book should be very useful.

Book reviews are grouped together and are indexed under that heading in alphabetical order under the letter B.

Abscess: See under names of organs and regions, as Lungs, abscess; etc.

Acidosis, diabetic, treatment of; comparison of methods with reference to use of racemic sodium lactate, 413

Acrocyanosis: See Cyanosis

Adams, M.: Idiopathic steatorrhea; metabolic study of patient with reference to utilization of nitrogen and fat, 1109

Adolescence, biologic effects of thymus extract (Hanson); accruing acceleration in growth and development in 5 successive generations of rats under continuous treatment with thymus extract, 1

Adrenalectomy: See under Suprarenals

Adrenals: See Suprarenals

Agranulocytosis: See Angina, agranulocytic

Alcohol, intraspinal injection in vascular diseases, 620

Allweiss, M. D.: Interpretation of abnormal dextrose tolerance curves occurring in toxemia in terms of liver function, 927

Althausen, T. L.: Carbohydrate intolerance and intestinal flora; clinical study based on 60 cases, 1263

Altow, H. O.: Renal amyloidosis; clinical course and pathologic lesions in 16 cases, 944

Amebiasis and amebic dysentery, review of current literature, 402

Amputations in vascular diseases, 620

Amyloidosis, renal, clinical course and pathologic lesions in 16 cases, 944

Andrews, E.: Bacteriology of normal and diseased gallbladders, 1171

Anemia, pernicious, following resection for gastric syphilis, 1049

Aneurysm, aortic; treatment of cardiovascular syphilis; study of duration of life in 80 treated and untreated patients with aortic aneurysm and aortic regurgitation, 773

pulmonary, 1221

pulmonary, dissecting, 1224

pulmonary, types of, 1222

Angina, agranulocytic, review of current literature, 405

Vincent's (fusospirochetosis), review of current literature, 405

Angina Pectoris, circulatory changes; experimental study, 59

treatment of congestive heart failure and angina pectoris by total ablation of normal thyroid gland; sensitivity of man to epinephrine injected intravenously before and after total thyroidectomy, 38

Aortitis, syphilitic; treatment of cardiovascular syphilis; study of duration of life in 80 treated and untreated patients with aortic aneurysm and aortic regurgitation, 773

Aring, C. D.: Differential diagnosis between cerebral hemorrhage and cerebral thrombosis; clinical and pathologic study of 245 cases, 435

Arsenic, massive treatment of early syphilis, 1039

Arsphenamine: See also under Syphilis

dermatitis due to, 1034

determination of sensitivity to, 1035

hemorrhagic encephalitis due to, 1032

ocular damage due to, 1031

toxic hepatitis due to, 1033

Arteries: See also Aneurysm; Aortitis; Arteriosclerosis; Blood pressure; Blood vessels; Embolism; Endarteritis; Thrombosis; etc.

arteriotomy in vascular diseases, 609

arteriography, 557

coronary, syphilitic involvement of, 1050

coronary; theophylline in treatment of disease of coronary arteries, 1250

inflammation; specific and nonspecific types of arteritis, 574

pulmonary; Ayerza's disease, 1009

pulmonary; fibrosis of media, 997

Arteries—Continued

pulmonary; hyperplasia of intimal elastic tissue, 993

pulmonary; hypertrophy of media, 995

pulmonary; pathology of vessels of pulmonary circulation, 211, 457, 724, 976, 1189

pulmonary; primary neoplasms, 1199

pulmonary; proliferation of intimal endothelium, 994

pulmonary, rheumatism of, 1190

pulmonary; secondary neoplasm, 1199

pulmonary; septic inflammation of pulmonary vessels, 1195

pulmonary, syphilis of, 999

pulmonary, tuberculosis, 1189

pulmonary, tumor embolism of, 1199

Arteriosclerosis, 568

pathology of vessels of pulmonary circulation, 211, 457, 724, 976, 1189

Arteritis: See Arteries, inflammation

Arthritis, chronic infectious, review of current literature, 388

Asthma, relation to sinusitis with reference to results from surgical treatment, 779

Atrophy, muscular, 1290

Ayerza's Disease: See Arteries, pulmonary

Bacilli: See Bacteria

Bacteria, microbial dissociation, review of current literature, 409

micrococci, review of current literature, 407

Streptococci: See Streptococci

Baker, M.: Infection and hemorrhagic nephritis, 297

Baldridge, C. W.: Cost of work in patients with hypermetabolism due to leukemia and to exophthalmic goiter, 30

Beard, H. H.: Cancer as problem in metabolism, 1143

Berger, S. S.: Pulmonary abscess and pulmonary gangrene; analysis of 90 cases observed in 10 years, 753

Bernstein, A.: Tularemia; report of 3 fatal cases with autopsies, 1117

Biliary Tract: See also Gallbladder; Liver hyperglycemia and glycosuria associated with disease of biliary tract, 1097

Blood cholesterol; effect of low caloric diets and resultant loss in weight on plasma cholesterol in obese, 884

circulation; obstructing pericarditis: effect of resection of pericardium on circulation of patient with concretion cordis, 250

circulation; pathology of vessels of pulmonary circulation, 211

circulatory changes in angina pectoris; experimental study, 59

Diseases: See Anemia; Leukemia; etc.

fibrin; fibrinolysis by streptococci, review of current literature, 408

normal hematologic standards, 849

oxygen tension, 556

pressure, effect of high intrapleural pressure on, 904

pressure, high, rôle of pressor substances in, 864

sugar, hyperglycemia and glycosuria associated with disease of biliary tract, 1097

transfusion and syphilis, 1042

vessels; arteriovenous anastomoses, 534

vessels, diseases, diagnostic methods, 543

vessels, diseases, surgical treatment; critical review, 605

vessels, diseases, treatment, 596

vessels, nerve supply, 536

vessels, pathology of vessels of pulmonary circulation, 211, 457, 724, 976, 1189

vessels; peripheral vascular diseases; review of recent literature with critical review of surgical treatment, 530

vessels, reaction to histamine, 552

Blumgart, H. L.: Treatment of congestive heart failure and angina pectoris by total ablation of normal thyroid gland; sensitivity of man to epinephrine injected intravenously before and after total thyroidectomy, 38

BOOK REVIEWS:

- Blood Groups and Blood Transfusions; A. S. Wiener, 1298
- Brain as an Organ: Its Postmortem Study and Interpretation; Frederic Wertham and Florence Wertham, 412
- Chemistry of the Hormones; B. Harrow and C. P. Sherwin, 1066
- Chirurgie du pancréas; P. Brocq and S. Miglinac, 831
- Clinical Aspects of Visceral Neurology, with Special Reference to Surgery of Sympathetic Nervous System; W. K. Livingston, 1066
- Diabetes Mellitus and Obesity; G. G. Duncan, 625
- Diabetic Manual for Patients; H. J. John, 210
- Dietetics for the Clinician; M. A. Bridges, 412
- Diseases of the Chest; J. A. Myers, 832
- Diseases of Children, with Contributions by 36 Authors; edited by H. Thursfield and D. Paterson, 626
- Erbpathologie: Ein Lehrbuch für Aerzte; O. Freiherr von Verschuer, 623
- Grundzüge der pathologischen Physiologie; H. Lueke, 832
- Heart Visible; J. Polevski, 210
- Illustrative Electrocardiography; J. H. Bainton and J. Burstein, 1300
- Klinik und Therapie der Herzkrankheiten; D. Scherf, 1299
- Memoirs of a Small-Town Surgeon; J. B. Wheeler, 624
- Methods of Treatment; L. Clendening, 626
- Nervous Patient; C. P. Emerson, 625
- Patient and Weather: Vol. II. Autonomic Disintegration; W. F. Petersen, 207
- Physiology in Modern Medicine; J. J. R. Macleod, 624
- Radiologie clinique du tube digestif: I. Estomac-duodénum; P. Duval, J. C. Roux and H. Bèlère, 1298
- Relation Between Vitamin B Requirements and Relative Quantity of Proteins; Fats and Carbohydrates in the Diet; P. Vogt-Møller, 1300
- Revista argentina de cardiologia, 209
- Rheumaprobleme: Vol. III. Gesammelte Vorträge gehalten auf dem III. Ärztekursus des Rheuma-Forschungs-Instituts am Landesbad der Rheinprovinz in Aachen, 209
- Sex Hygiene: What to Teach and How to Teach It; A. Worcester, 208
- Textbook of Biochemistry; B. Harrow and C. P. Sherwin, 210
- Treatment by Diet; C. J. Barborka, 210
- Venarum Ostiolis 1603 of Hieronymus Fabricius ab Aquapendente (1537-1619); facsimile edition with Introduction, translation and notes by K. J. Franklin, 208
- Boothby, W. M.: Disease of thyroid gland; interpretative review of progress toward solution of problem, 136; correction, 1065
- Brain, differential diagnosis between cerebral hemorrhage and cerebral thrombosis; clinical and pathologic study of 245 cases, 435
- electro-encephalography, 1291
- Brenner, O.: Pathology of vessels of pulmonary circulation, 211, 457, 724, 976, 1189
- Briard, S. P.: Cost of work in patients with hypermetabolism due to leukemia and to exophthalmic goiter, 30
- Bright's Disease: See Nephritis
- Bruger, M.: Effect of low caloric diets and resultant loss in weight on plasma cholesterol in obese, 884
- Burwell, C. S.: Obstructing pericarditis; effect of resection of pericardium on circulation of patient with concretio cordis, 250
- Byron, C. S.: Influence of di-nitrophenol on carbohydrate metabolism, 374
- Calhoun, J. A.: Effect of diuretics on cardiac output of patients with congestive heart failure, 341
- Cancer: See also under names of organs and regions
- Cancer—Continued
- as problem in metabolism, 1143
- review of current literature, 396
- Cantarow, A.: Studies of hepatic function in portal cirrhosis and congestive heart failure, 521
- Capillaries, circulation, 531
- Capps, R. B.: Role of pressor substances in arterial hypertension, 864
- Carbohydrate Intolerance and Intestinal flora; clinical study based on 60 cases, 1263
- metabolism, influence of di-nitrophenol on, 374
- Carbon tetrachloride poisoning, acute, report of case, 98
- Cardiovascular Diseases: See also Blood vessels; Heart
- in trichinosis, 238
- syphilis, 1049
- syphilis; effect of antisyphilitic treatment in prolonging life, 1051
- syphilis; study of duration of life in 80 treated and untreated patients with aortic aneurysm and aortic regurgitation, 773
- Cardiovascular System: See Arteries; Blood vessels; Heart; etc.
- Carr, J. G.: Clinical experience with derivative of quill, 700
- Castle, W. B.: Etiology and treatment of sprue; observations on patients in Puerto Rico and subsequent experiments on animals, 627
- Celiac Disease, Idiopathic steatorrhea; metabolic study of patient with reference to utilization of nitrogen and fat, 1109
- Central Society for Clinical Research, meeting, 832
- Cerebrospinal fluid in syphilis, 1036
- Charles, C. M.: Differential diagnosis of rubella; use of Schilling differential leukocyte count, 935
- Cheney, G.: Appearance of dengue-like fever in Northern California, 1067
- Gastro-enterology in 1934, 797
- Cholecystitis: See under Gallbladder
- Cholesteraemia: See Blood, cholesterol
- Chordotomy in vascular diseases, 620
- Clark, B. B.: Increased effectiveness of insulin when given by injections of doses of equal unitage at intervals of 2 to 4 hours; use of insulin in divided doses to manage severe uncomplicated diabetes and to control complicated medical cases, 360
- Clark, G.: Effect of digitalis on cardiac output of persons with congestive heart failure, 710
- Clark, J. H.: Biologic effects of thymus extract (Hanson); accruing acceleration in growth and development in 5 successive generations of rats under continuous treatment with thymus extract, 1
- Clutton's Joints: See Knee, syphilis
- Cobb, S.: Review of neuropsychiatry, 1287
- Cohen, E.: Teaching medical students objectives for care of patients and social aspects of illness, 351
- Cold, urticaria due to sensitivity to cold; survey of literature and report of case with experimental observations, 498
- Colitis, ulcerative, review of current literature, 403
- Concretio Cordis: See Pericarditis
- Cooke, R. A.: Relation of asthma to sinusitis with reference to results from surgical treatment, 779
- Cyanosis, acrocyanosis, 591
- Deafness; nerve deafness due to syphilis, 1053
- Dementia Paralytica: See Paralysis, general
- Dengue; appearance of dengue-like fever in Northern California, 1067
- Dermatitis; pellagrous dermatitis and sunlight, 920
- Derow, H. A.: Teaching medical students objectives for care of patients and social aspects of illness, 351
- de Takáts, G.: Peripheral vascular diseases; review of recent literature with critical review of surgical treatment, 530

- Dextrose; Interpretation of abnormal dextrose tolerance curves occurring in toxemia in terms of liver function, 927
renal threshold for dextrose in man, 877
- Diabetes Mellitus, hyperglycemia and glycosuria associated with disease of biliary tract, 1097
increased effectiveness of insulin when given by injections of doses of equal unitage at intervals of 2 to 4 hours; use of insulin in divided doses to manage severe uncomplicated diabetes and to control complicated medical cases, 360
treatment of severe diabetic acidosis; comparison of methods with reference to use of racemic sodium lactate, 413
- Digestive Tract: See Gastro-enterology; Intestines; Stomach; etc.
- Digitalis: See under Heart
- Di-Nitrophenol: See Nitrophenol
- Diuretics: See also Theophylline
effect on cardiac output of patients with congestive heart failure, 341
- Dock, W.: Experimental concentric and eccentric cardiac hypertrophy in rats, 511
- Duodenum, progress in gastro-enterology in 1934, 817
Ulcer: See Peptic Ulcer
- Dysentery, Amebic: See Amebiasis
bacillary, review of current literature, 403
- Dystrophy, muscular, 1290
- Edema, effect of diuretics on cardiac output of patients with congestive heart failure, 341
- Education, medical; teaching medical students objectives for care of patients and social aspects of illness, 351
- Electrocardiogram: See under Heart
- Electro-encephalography, 1291
- Embolectomy, 617
- Embolism, arterial, 572
tumor embolism of pulmonary arteries, 1199
- Emphysema, pathology of vessels of pulmonary circulation, 234
- Empyema, pyothorax due to fusospirochetal infection, 790
- Encephalitis, hemorrhagic, due to arsphenamine, 1032
review of current literature, 394
- Endarteritis obliterans of pulmonary vessels, 990
- Epilepsy, 1292
- Epinephrine: See Suprarenal Preparations
- Erythema arthriticum epidemicum, review of current literature, 406
- Erythromalgia, 587
- Esophagus, progress in gastro-enterology, 797
- Eyes, damage due to arsphenamine, 1031
effect of trypanamide on, 1056
- Fecundity, biologic effects of thymus extract (Hanson); accruing acceleration in growth and development in 5 successive generations of rats under continuous treatment with thymus extract, 1
- Ferris, E. B., Jr.: Role of pressor substances in arterial hypertension, 864
- Fertility: See Fecundity
- Fetus, experimental syphilis in, 1043
- Fever, appearance of dengue-like fever in Northern California, 1067
Therapeutic: See also under Malaria
therapeutic; physiology of electroprexia, 1061
- Fibrinolysis: See Blood, fibrin
- Flack, R. A.: Pyothorax due to fusospirochetal infection, 790
- Flickinger, D.: Obstructing pericarditis; effect of resection of pericardium on circulation of patient with concretion cords, 250
- Fowler, W. M.: Effect of theophylline ethylenediamine on experimentally induced cardiac infarction in dog, 1242
- Friedgood, H. B.: Cyclic response of thyroid gland to experimental excitation and depression, 833
- Friedman, B.: Effect of certain therapeutic measures on cardiac output of patients with congestive heart failure, 891
Effect of digitalis on cardiac output of persons with congestive heart failure, 710
Effect of diuretics on cardiac output of patients with congestive heart failure, 341
- Fusospirochetosis: See Angina, Vincent's; Spirochetosis
- Gallbladder: See also Biliary Tract
bacteriology of normal and diseased gallbladders, 1171
hyperglycemia and glycosuria associated with disease of biliary tract, 1097
- Ganglionectomy: See Sympathectomy
- Gangrene, gas, review of current literature, 406
pulmonary abscess and gangrene; analysis of 90 cases observed in 10 years, 753
- Gas Gangrene: See Gangrene
- Gastro-enterology in 1934, 797
- Gibson, R. B.: Increased effectiveness of insulin when given by injections of doses of equal unitage at intervals of 2 to 4 hours; use of insulin in divided doses to manage severe uncomplicated diabetes and to control complicated medical cases, 360
- Gilligan, D. R.: Treatment of congestive heart failure and angina pectoris by total ablation of normal thyroid gland; sensitivity of man to epinephrine injected intravenously before and after total thyroidectomy, 38
- Glomerulonephritis: See Nephritis, glomerular
- Goiter: See also Thyroid
exophthalmic; cost of work in patients with hypermetabolism due to leukemia and to exophthalmic goiter, 30
- Gonorrhea, review of current literature, 400
- Granulocytopenia: See Angina, agranulocytic
- Grove, R. C.: Relation of asthma to sinusitis with reference to results from surgical treatment, 779
- Growth, biologic effects of thymus extract (Hanson); accruing acceleration in growth and development in 5 successive generations of rats under continuous treatment with thymus extract, 1
- Gunnison, J. B.: Carbohydrate intolerance and intestinal flora; clinical study based on 60 cases, 1263
- Hanson, A. M.: Biologic effects of thymus extract (Hanson); accruing acceleration in growth and development in 5 successive generations of rats under continuous treatment with thymus extract, 1
- Harrison, T. R.: Effect of certain therapeutic measures on cardiac output of patients with congestive heart failure, 891
Effect of digitalis on cardiac output of persons with congestive heart failure, 710
Effect of diuretics on cardiac output of patients with congestive heart failure, 341
- Hartmann, A. F.: Treatment of severe diabetic acidosis; comparison of methods with reference to use of racemic sodium lactate, 413
- Haverhill Fever: See Erythema arthriticum epidemicum
- Head, J. R.: Effect of high intrapleural pressure on blood pressure, 904
- Headaches following lumbar puncture, 1036
- Heart: See also Blood, circulation; Myocarditis; Pericarditis; etc.
acute cardiac infarction involving anterior and posterior surfaces of left ventricle; electrocardiographic characteristics, 77
Blood Supply: See Arteries, coronary; Thrombosis
cardiovascular complications of trichinosis, 238
congestive heart failure, effect of certain therapeutic measures on cardiac output of patients with, 891
congestive heart failure, effect of digitalis on cardiac output of persons with, 710
congestive heart failure, effect of diuretics on cardiac output of patients with, 341
congestive heart failure; studies of hepatic function in portal cirrhosis and congestive heart failure, 521
congestive heart failure; treatment of congestive heart failure and angina pectoris by total ablation of normal thyroid gland; sensitivity of man to epinephrine injected intravenously before and after total thyroidectomy, 38
decompensation, scillonin in; clinical experience with derivative of squill, 700

Heart—Continued

- disease, theophylline in treatment of disease of coronary arteries, 1250
hypertrophy; experimental concentric and eccentric cardiac hypertrophy in rats, 511
Infarction: See also Thrombosis
infarction; effect of theophylline ethylenediamine on experimentally induced cardiac infarction in dog, 1242
pathology of vessels of pulmonary circulation, 211
stab wounds of; study of electrocardiographic changes, polyserositis (Pick's syndrome) and pericarditis, 281
syphilis; thyroidectomy in advanced syphilitic cardiac disease, 1051
Hemato-Encephalic Barrier: See Meninges, permeability
Hematopoietic System, normal hematologic standards, 849
Hemophilus Pertussis: See Whooping Cough
Henry, L. D.: Bacteriology of normal and diseased gallbladders, 1171
Hepatitis: See under Liver
Histamine, reaction of blood vessels to, 552
Histoplasmosis, review of current literature, 406
Hormones, rôle of pressor substances in arterial hypertension, 864
Hurevitz, H. M.: Effect of theophylline ethylenediamine on experimentally induced cardiac infarction in dog, 1242
Hypertension: See Blood pressure, high
Hyperthermia: See under Fever
Hyperthyroidism: See Thyroid, hyperthyroidism
Hypoglycemia: See Blood, sugar

Industry and Occupations; disease of persons using pneumatic hammer, 587

- Infection and hemorrhagic nephritis, 297
Infectious diseases; review of current literature, 382
Influenza, review of current literature, 385
Insulin: See Diabetes Mellitus
International Congress of History of Medicine, 412
Intestines, flora; carbohydrate intolerance and intestinal flora; clinical study based on 60 cases, 1263
progress in gastro-enterology in 1934, 820, 825

Kane, A. P.: Influence of di-nitrophenol on carbohydrate metabolism, 374

- Kepler, E. J.: Diseases of adrenal glands; review with reference to clinical aspects, 105
Keratitis, interstitial, in syphilis, 1044
Kidneys, amyloidosis; clinical course and pathologic lesions in 16 cases, 944
Diseases: See Nephritis
function, effect of antisyphilitic treatment on, 1031
function; renal threshold for dextrose in man, 877
Insufficiency; experimental concentric and eccentric cardiac hypertrophy in rats, 511
Kilne, B. S.: Pulmonary abscess and pulmonary gangrene; analysis of 90 cases observed in 10 years, 753
Knee, syphilis, 1045
Koucky, J. D.: Stab wounds of heart; study of electrocardiographic changes, polyserositis (Pick's syndrome) and pericarditis, 281

Lande, H.: Hyperglycemia and glycosuria associated with disease of biliary tract, 1097

- Lawson, H. A.: Etiology and treatment of sprue; observations on patients in Puerto Rico and subsequent experiments on animals, 627
Lehnher, E. R.: Acute carbon tetrachloride poisoning; report of case, 98
Leprosy, review of current literature, 404
Leukemia, cost of work in patients with hypermetabolism due to leukemia and to exophthalmic goiter, 30
Levine, H. D.: Urticaria due to sensitivity to cold; survey of literature and report of case with experimental observations, 498
Liver: See also Biliary Tract
function in portal cirrhosis and congestive heart failure, 521

Liver—Continued

- function, interpretation of abnormal dextrose tolerance curves occurring in toxemia in terms of, 927
toxic hepatitis due to arsphenamine, 1033
Lumbar Puncture: See Spinal Puncture
Lungs: See also Arteries, pulmonary
abscess and gangrene; analysis of 90 cases observed in 10 years, 753
endarteritis obliterans of, 990
fibrosis; pathology of vessels of pulmonary circulation, 235
pathology of vessels of pulmonary circulation, 211, 457, 724, 976, 1189
primary vascular sclerosis, 976
Lymph nodes, glandular transfer as evidence of cure of syphilis, 1040

MacBryde, C. M.: Differential diagnosis of rubella; use of Schilling differential leukocyte count, 935

- McClintock, J. T.: Cost of work in patients with hypermetabolism due to leukemia and to exophthalmic goiter, 30
MacKay, E. M.: Renal threshold for dextrose in man, 877
McLeod, N.: Infection and hemorrhagic nephritis, 297
Malaria, therapeutic, in treatment of syphilis, 1063
therapeutic, untoward effects of, 1064
therapeutic; use of malaria in treatment of drug-resistant syphilis, 1036
treatment of, 1064
Maly, H. W.: Renal amyloidosis; clinical course and pathologic lesions in 16 cases, 944
Mapharsen in syphilis, 1064
Marshall, M. S.: Carbohydrate intolerance and intestinal flora; clinical study based on 60 cases, 1263
Mayer, J. D.: Clinical experience with derivative of squill, 700
Meninges, permeability; blood spinal fluid barrier in syphilis, 1037
Meningitis, meningococcal, review of current literature, 401
Merritt, H. H.: Differential diagnosis between cerebral hemorrhage and cerebral thrombosis, clinical and pathologic study of 245 cases, 435
Metabolism, basal; cost of work in patients with hypermetabolism due to leukemia and to exophthalmic goiter, 30
cancer as problem in, 1143
Meyer, J.: Action of oil of peppermint on secretion and motility of stomach in man, 88
Migraine, 1294
Milles, G.: Stab wounds of heart; study of electrocardiographic changes, polyserositis (Pick's syndrome) and pericarditis, 281
Mirsky, I. A.: Interpretation of abnormal dextrose tolerance curves occurring in toxemia in terms of liver function, 927
Moore, J. E.: Syphilis; review of recent literature, 1015
Morton, M.: Treatment of severe diabetic acidosis; comparison of methods with reference to use of racemic sodium lactate, 413
Mumps: See Parotitis
Muscles, atrophy and dystrophy (myopathy), 1290
Myocarditis, acute, subacute and chronic isolated myocarditis; report of case, 1136
Myositis, epidemic, review of current literature on pleurodynia, 407
Nechefes, H.: Action of oil of peppermint on secretion and motility of stomach in man, 88
Nephritis, glomerular; acute glomerulonephritis following pneumococcal lobar pneumonia; analysis of 7 cases, 912
hemorrhagic, and infection, 297
Nerve block, paravertebral block in vascular diseases, 620
block, peripheral, in vascular diseases, 619
eighth, involvement in syphilis, 1053
optic, atrophy, treatment in syphilis, 1054
Neuropsychiatry, review of, 1287

INDEX TO VOLUME 56

- Neuroses and Psychoneuroses; psychoneurosis, 1296
- Neurosyphilis: See under Syphilis
- Nitrophenol, influence of di-nitrophenol on carbohydrate metabolism, 374
- Nose, Accessory Sinuses: See Sinuses
- Obesity, effect of low caloric diets and resultant loss in weight on plasma cholesterol in obese, 884
- Oscillometry in diagnosis of diseases of blood vessels, 550
- Osgood, E. E.: Normal hematologic standards, 849
- Pain, referred; viscerogalvanic reaction, 327
- Paralysis, general; juvenile dementia paralytica, 1045
- Parotitis, treatment, 1294
- Patients: See Physicians, relation to patient
- Paul, W. D.: Increased effectiveness of insulin unitage at intervals of 2 to 4 hours; use of insulin in divided doses to manage severe uncomplicated diabetes and to control severe complicated medical cases, 360
- Theophylline in treatment of disease of coronary arteries, 1250
- Payne, G. C.: Etiology and treatment of sprue; observations on patients in Puerto Rico and subsequent experiments on animals, 627
- Pellagra, relationship of pellagrous dermatitis to sunlight, 920
- Peppermint oil, action on secretion and motility of stomach in man, 88
- Peptic Ulcer, 810
- action of oil of peppermint on secretion and motility of stomach in man, 88
- Periarteritis nodosa, 1199
- Pericarditis, obstructing effect of resection of pericardium on circulation of patient with stab wounds of heart; study of electrocardiographic changes, polyserositis (Pick's syndrome) and pericarditis, 281
- Pertussis: See Whooping cough
- Phenolsulphonphthalein Test: See Kidneys, function
- Phlebitis, latent, 594
- Physicians, relation to patient; teaching medical students objectives for care of patients and social aspects of illness, 351
- Pick's syndrome, stab wounds of heart, polyserositis (Pick's syndrome) and pericarditis, 281
- Plethysmographs in diagnosis of diseases of blood vessels, 551
- Pleura, adhesions; pathology of vessels of pulmonary circulation, 235
- effect of high intrapleural pressure on blood pressure, 904
- Pleurodynia: See Myositis, epidemic
- Pneumatic hammer, disease from using, 587
- Pneumonia, acute glomerulonephritis following pneumococcal lobar pneumonia; analysis of 7 cases, 912
- review of current literature, 382
- Poindexter, C. A.: Effect of low caloric diets and resultant loss in weight on plasma cholesterol in obese, 884
- Poliomyelitis, review of current literature, 393
- Pollack, H.: Hyperglycemia and glycosuria associated with disease of biliary tract, 1097
- Polyserositis: See Pick's syndrome
- Pregnancy and syphilis, 1042
- Psittacosis, review of current literature, 407
- Psychoneurosis: See Neuroses and Psychoneuroses
- Puberty: See Adolescence
- Pyothorax due to fusospirochetal infection, 790
- Rathe, H. W.: Theophylline in treatment of disease of coronary arteries, 1250
- Reflexes; viscerogalvanic reaction, 327
- Reimann, H. A.: Infectious diseases; review of current literature, 382
- Reisner, D.: Pulmonary tuberculosis of lower lobe, 258
- Resnik, H., Jr.: Effect of certain therapeutic measures on cardiac output of patients with congestive heart failure, 891
- Effect of digitalis on cardiac output of persons with congestive heart failure, 710
- Effect of diuretics on cardiac output of patients with congestive heart failure, 341
- Rheumatic fever, review of current literature, 386
- Rheumatism of pulmonary arteries, 1190
- Rhoads, C. P.: Etiology and treatment of sprue; observations on patients in Puerto Rico and subsequent experiments on animals, 627
- Riseman, J. E. F.: Treatment of congestive heart failure and angina pectoris by total ablation of normal thyroid gland; sensitivity of man to epinephrine injected intravenously before and after total thyroidectomy, 38
- Rowntree, L. G.: Biologic effects of thymus extract (Hanson); accruing acceleration in growth and development in 5 successive generations of rats under continuous treatment with thymus extract, 1
- Rubella, differential diagnosis of; use of Schilling differential leukocyte count, 935
- Ryland, D. A.: Experimental concentric and eccentric cardiac hypertrophy in rats, 511
- Salyrgan: See Diuretics
- Schelman, L.: Action of oil of peppermint on secretion and motility of stomach in man, 88
- Schilling differential leukocyte count, 935
- Schillonin, clinical experience with derivative of squill, 700
- Sclerosis, multiple, 1295
- secondary pulmonary vascular sclerosis, 724
- Seupham, G. W.: Peripheral vascular diseases; review of recent literature with critical reference to surgical treatment, 530
- Seegal, D.: Acute glomerulonephritis following pneumococcal lobar pneumonia; analysis of 7 cases, 912
- Shambaugh, P.: Circulatory changes in angina pectoris; experimental study, 59
- Sherrill, J. W.: Renal threshold for dextrose in man, 877
- Shipman, S. J.: Carbohydrate intolerance and intestinal flora; clinical study based on 60 cases, 1263
- Shlevin, E. L.: Influence of di-nitrophenol on carbohydrate metabolism, 374
- Simon, M. A.: Acute, subacute, and chronic isolated myocarditis; report of case, 1136
- Sinuses, relation of asthma to sinusitis with reference to results from surgical treatment, 779
- Skin, temperature; functions of vasoconstriction and vasodilatation, 540
- viscerogalvanic reaction, 327
- Smith, F. M.: Effect of theophylline ethylenediamine on experimentally induced cardiac infarction in dog, 1242
- Theophylline in treatment of disease of coronary arteries, 1250
- Social service; teaching medical students objectives for care of patients and social aspects of illness, 351
- Societies, Tenth International Congress of History of Medicine, 412
- Sodium lactate, treatment of severe diabetic acidosis; comparison of methods with reference to use of racemic sodium lactate, 413
- Soskin, S.: Interpretation of abnormal dextrose tolerance curves occurring in toxemia in terms of liver function, 927
- Spiegel, E. A.: Viscerogalvanic reaction, 327
- Spies, T. D.: Relationship of pellagrous dermatitis to sunlight, 920
- Spinal Puncture, complications of, 1037
- Spink, W. W.: Cardiovascular complications of trichinosis, 238
- Spirochaeta pallida, 1016
- Spirochetosis, pyothorax due to fusospirochetal infection, 790
- review of current literature on fusospirochetosis, 405

- Sprue, etiology and treatment; observations on patients in Puerto Rico and subsequent experiments on animals, 627
- Nontropical: See Celiac Disease
- Squill, clinical experience with derivative of, 700
- Steatorrhea, Idiopathic: See Celiac Disease
- Steinberg, A.: Biologic effects of thymus extract (Hanson); accruing acceleration in growth and development in 5 successive generations of rats under continuous treatment with thymus extract, 1
- Stomach, action of oil of peppermint on secretion and motility of stomach in man, 88
- progress in gastro-enterology in 1934, 800
- syphilis, 1048
- syphilis, pernicious anemia following resection for, 1049
- Ulcer: See Peptic Ulcer
- Stratton, E. K.: Treatment of cardiovascular syphilis; study of duration of life in 80 treated and untreated patients with aortic aneurysm and aortic regurgitation, 773
- Streptococci, fibrinolysis by; review of current literature, 408
- Sugar in Blood: See Blood, sugar
- in Urine: See Urine, sugar
- Sunlight, relationship of pellagrous dermatitis to, 920
- Suprarenal Preparations, treatment of congestive heart failure and angina pectoris by total ablation of normal thyroid gland; sensitivity of man to epinephrine injected intravenously before and after total thyroidectomy, 38
- Suprarenals, adrenalectomy and adrenal denervation in vascular disease, 618
- diseases; review with reference to clinical aspects, 105
- Sympathectomy, periarterial, in vascular diseases, 607
- sympathetic ganglionectomy in vascular diseases, 611
- sympathetic ramisection in vascular diseases, 610
- Syphilis: See also under names of organs and regions, as, Arteries; Cardiovascular Diseases, syphilis; Kneec, syphilis; Heart, syphilis; Stomach, syphilis; and under names of diseases, as, Aortitis, syphilitic; etc.
- acetarsone treatment of neurosyphilis, 1055
- and blood transfusion, 1042
- and pregnancy, 1042
- arsenical treatment of early syphilis, 1039
- benign late, treatment of, 1041
- blood-spinal fluid barrier in, 1037
- carriers, 1041
- cellular pathology of, 1020
- cerebrospinal fluid in, 1036
- congenital, 1042
- congenital, acetarsone in, 1047
- drugs used in, 1026
- epidemiology, 1025
- fetal, experimental, 1043
- fever therapy, 1056
- fever therapy of neurosyphilis with vaccine, 1062
- glandular transfer as evidence of cure, 1040
- interstitial keratitis in, 1044
- malarial therapy, 1063
- malarial therapy of drug-resistant syphilis, 1036
- malarial therapy of neurosyphilis, results of, 1062
- malarial therapy, untoward effects, 1064
- neurosyphilis, 1052
- review of recent literature, 1015
- serodiagnosis; American Serologic Conference, 1021
- subdural treatment of neurosyphilis, 1053
- toxic reactions due to drugs, 1031
- treatment in early syphilis, 1038
- tryparsamide and acetarsone in treatment of neurosyphilis, 1055
- Taylor, F. H. L.: Role of pressor substances in arterial hypertension, 864
- Tetanus, review of current literature, 392
- Theophylline ethylenediamine, effect on experimentally induced cardiac infarction in dog, 1242
- in treatment of disease of coronary arteries, 1250
- Thrombo-angitis obliterans, 559
- Thrombophilia, essential, 568
- Thrombosis, coronary; acute cardiac infarction involving anterior and posterior surfaces of left ventricle; electrocardiographic characteristics, 77
- differential diagnosis between cerebral hemorrhage and cerebral thrombosis; clinical and pathologic study of 245 cases, 435
- induced by effort, 593
- of large intrapulmonary branches, 1208
- of main right and left pulmonary arteries, 1206
- of pulmonary vessels, 1203
- of small muscular arteries, 1214
- Thymus extract (Hanson), biologic effects; accruing acceleration in growth and development in 5 successive generations of rats under continuous treatment with thymus extract, 1
- Thyroid: See also Goiter
- cyclic response to experimental excitation and depression, 833
- diseases; Interpretative review of progress toward solution of problem, 136; correction, 1065
- excision; thyroidectomy in advanced syphilitic cardiac disease, 1051
- excision; treatment of congestive heart failure and angina pectoris by total ablation of normal thyroid gland; sensitivity of man to epinephrine injected intravenously before and after total thyroidectomy, 38
- hyperthyroidism; experimental concentric and eccentric cardiac hypertrophy in rats, 511
- Thyroidectomy: See Thyroid, excision
- Toxemia, Interpretation of abnormal dextrose tolerance curves occurring in toxemia in terms of liver function, 927
- Trichinosis, cardiovascular complications, 238
- Tryparsamide: See also under Syphilis
- effect on eye, 1056
- Tuberculosis, pulmonary, of lower lobe, 258
- review of current literature, 390
- Tularemia, report of 3 fatal cases with autopsies, 1117
- Typhus, review of current literature, 397
- Urine, rôle of pressor substances in arterial hypertension, 864
- sugar; hyperglycemia and glycosuria associated with disease of biliary tract, 1097
- sugar; renal threshold for dextrose in man, 877
- Urticaria due to sensitivity to cold; survey of literature and report of case with experimental observations, 498
- Van Winkle, C. C.: Renal amyloidosis; clinical course and pathologic lesions in 16 cases, 944
- Venous Pressure: See under Blood
- Vincent's Angina: See Angina
- Viscera; viscerogalvanic reaction, 327
- Weir, J. F.: Idiopathic steatorrhea; metabolic study of patient with reference to utilization of nitrogen and fat, 1109
- Welss, S.: Rôle of pressor substances in arterial hypertension, 864
- Whooping cough, review of current literature, 404
- Williams, L. E.: Renal amyloidosis; clinical course and pathologic lesions in 16 cases, 944
- Winkenwerder, W. L.: Infection and hemorrhagic nephritis, 297
- Wishnoffsky, M.: Influence of di-nitrophenol on carbohydrate metabolism, 374
- Wohl, M. G.: Viscerogalvanic reaction, 327
- Wolfertz, C. C.: Acute cardiac infarction involving anterior and posterior surfaces of left ventricle; electrocardiographic characteristics, 77
- Wolpaw, S.: Acute, subacute and chronic isolated myocarditis; report of case, 1136
- Wood, F. C.: Acute cardiac infarction involving anterior and posterior surfaces of left ventricle; electrocardiographic characteristics, 77
- Work, cost in patients with hypermetabolism due to leukemia and to exophthalmic goiter, 30
- Yellow fever, review of current literature, 404

